[JP,2006-176407,A]

Japanese (PDF) | File Wrapper Information

FULL CONTENTS CLAIM + DETAILED DESCRIPTION TECHNICAL FIELD PRIOR ART EFFECT OF THE INVENTION TECHNICAL PROBLEM MEANS EXAMPLE DESCRIPTION OF DRAWINGS DRAWINGS

[Translation done.]

CLAIM + DETAILED DESCRIPTION

[Claim(s)]
[Claim 1]
Following formula (I) :
[Chemical formula 1]

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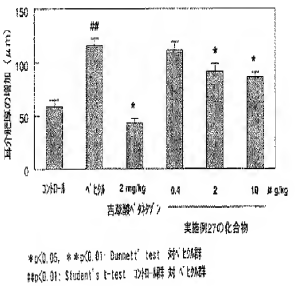

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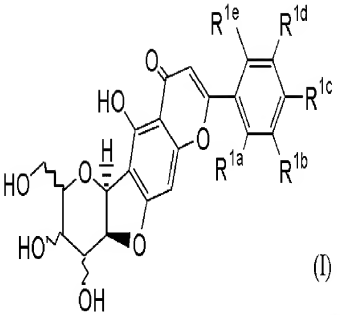


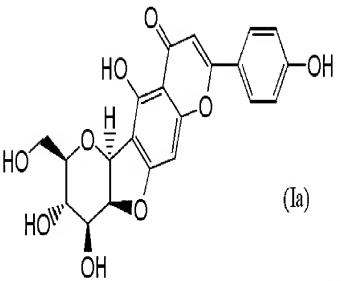
(I)

(R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} express independently an alkyl group or a halogen atom of a straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, an alkoxy group of branched chain and a straight chain of the carbon numbers 1-6, or branched chain among a formula, respectively)

The compound come out of and expressed, and its salt permitted pharmacologically.

However, following formula (Ia) :

[Chemical formula 2]



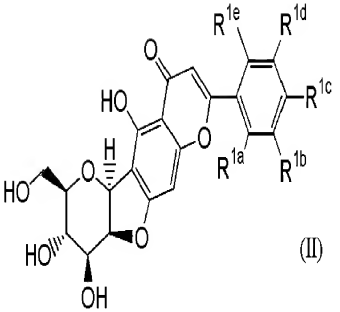
(Ia)

It comes out and the compound expressed or its salt permitted pharmacologically is excluded.

[Claim 2]

Following formula (II) :

[Chemical formula 3]



(II)

(R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} express independently an alkyl group or a halogen atom of a straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, an alkoxy group of branched chain and a straight chain of the carbon numbers 1-6, or branched chain among a formula, respectively)

A compound come out of and expressed, and its salt permitted pharmacologically. However, R^{1c} is a hydroxyl group and R^{1a}, R^{1b}, R^{1d}, and R^{1e} remove a compound which is a hydrogen atom, or its salt permitted pharmacologically.

[Claim 3]

The compound according to claim 2 by which R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are expressed with formula (II) which is a hydrogen atom, respectively, and its salt permitted pharmacologically.

[Claim 4]

The compound according to claim 2 by which R^{1a}, R^{1b}, R^{1d}, and R^{1e} are hydrogen atoms, respectively, and R^{1c} is expressed with formula (II) which is a methyl group, and its salt permitted pharmacologically.

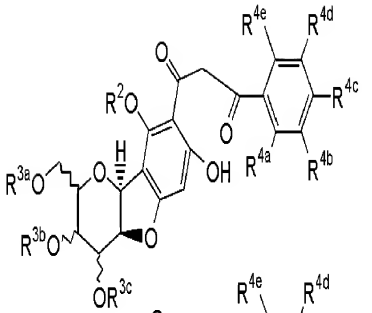
[Claim 5]

The compound according to claim 2 by which R^{1a}, R^{1b}, R^{1d}, and R^{1e} are hydrogen atoms, respectively, and R^{1c} is expressed with formula (II) which is a methoxy group, and its salt permitted pharmacologically.

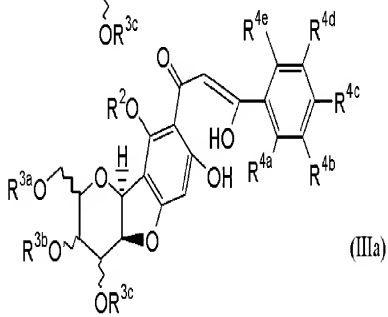
[Claim 6]

A following formula which are following formula (III) and its tautomer (IIIa) :

[Chemical formula 4]



(III)

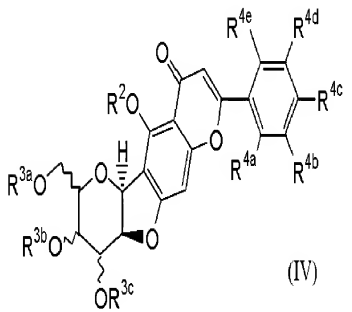


(IIIa)

R^{3a}, R^{3b}, and R^{3c} express a protective group of a hydroxyl group among [type, R^2 expresses a protective group of a hydrogen atom or a hydroxyl group, and, [R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e}]] which expresses independently an alkyl group of a straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, an alkoxy group of branched chain and a straight chain of the carbon numbers 1-6, or branched chain, an R^5-O-group (R^5 expresses a protective group of a hydroxyl group), or a halogen atom, respectively

Come out, an acid is made to act to the compound expressed, and it is following formula (IV). :

[Chemical formula 5]

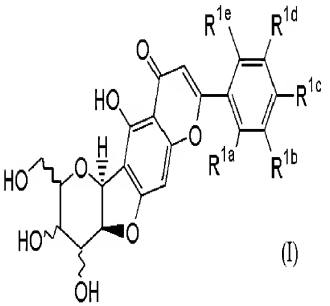


(IV)

(The inside of a formula, R^2, R^{3a}, R^{3b}, R^{3c}, R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e} are the same as that of said definition)

Following formula (I) carrying out deprotection, and refining if required after coming out and considering it as the compound expressed :

[Chemical formula 6]



(I)

(R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} express independently the alkyl group or halogen atom of the straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, the alkoxy group of branched chain and the straight chain of the carbon numbers 1-6, or branched chain among a formula, respectively)

A manufacturing method of a compound come out of and expressed.

[Claim 7]

A compound denoted by a general formula (IIIa) which are general formula (III) indicated to Claim 6, and its tautomer.

[Claim 8]

A compound whose R^2 is a methyl group in a formula (IIIa) which are formula (III) indicated to Claim 6, and its tautomer and whose R^{3a}, R^{3b}, and R^{3c} are benzyls.

[Claim 9]

A compound denoted by formula (IV) indicated to Claim 6.

[Claim 10]

A compound which is indicated to Claim 6, whose R^2 formula (IV) sets and is a methyl group and whose R^{3a}, R^{3b}, and R^{3c} are benzyls.

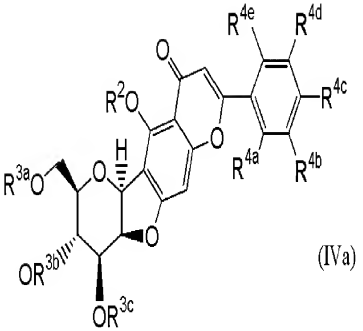
[Claim 11]

A compound which is indicated to Claim 6 and whose R^2, R^{3a}, R^{3b}, and R^{3c} formula (IV) sets and are acetyl groups.

[Claim 12]

A following formula (IVa) :

[Chemical formula 7]



(IVa)

R^{3a}, R^{3b}, and R^{3c} express the protective group of a hydroxyl group among [type, R^2 expresses the protective group of a hydrogen atom or a hydroxyl group, and, [R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e}]] which expresses independently the alkyl group of the straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, the alkoxy group of branched chain and the straight chain of the carbon numbers 1-6, or branched chain, an R^5-O-group (R^5 expresses the protective group of a hydroxyl group), or a halogen atom, respectively The compound come out of and expressed.

[Claim 13]

A compound whose R^2 is a methyl group in a formula (IVa) indicated to Claim 12 and whose R^{3a}, R^{3b}, and R^{3c} are benzyls.

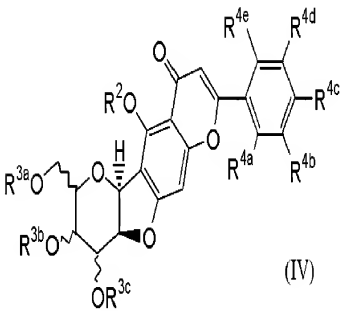
[Claim 14]

A compound whose R^2, R^{3a}, R^{3b}, and R^{3c} are acetyl groups in a formula (IVa) indicated to Claim 12.

[Claim 15]

Following formula (IV) :

[Chemical formula 8]

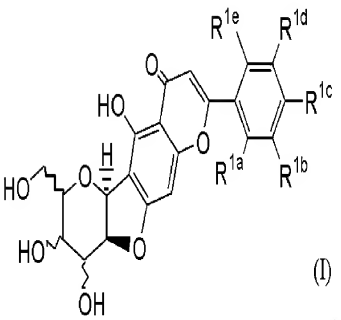


(IV)

R^{3a}, R^{3b}, and R^{3c} express the protective group of a hydroxyl group among [type, R^2 expresses the protective

group of a hydrogen atom or a hydroxyl group, and, [R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e}]] which expresses independently the alkyl group of the straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, the alkoxy group of branched chain and the straight chain of the carbon numbers 1-6, or branched chain, an R^5-O-group (R^5 expresses the protective group of a hydroxyl group), or a halogen atom, respectively It is following formula (I) by coming out, and carrying out deprotection of the protective group of a hydroxyl group, and refining to the compound expressed, if required. :

[Chemical formula 9]



(I)

(R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} express independently the alkyl group or halogen atom of the straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, the alkoxy group of branched chain and the straight chain of the carbon numbers 1-6, or branched chain among a formula, respectively)

A manufacturing method coming out and obtaining the compound expressed.

[Claim 16]

The manufacturing method according to claim 15 whose R^2 is a methyl group in formula (IV) and whose R^{3a}, R^{3b}, and R^{3c} are benzyls.

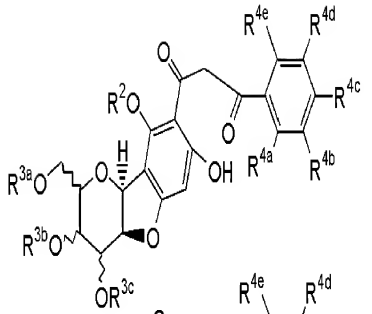
[Claim 17]

The manufacturing method according to claim 15 which performs deprotection of a hydroxyl group by BCl_3.

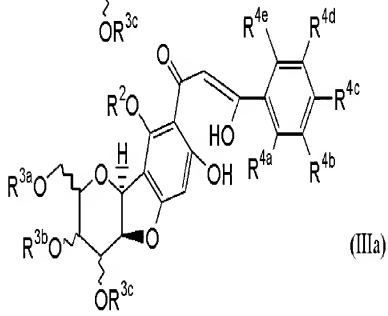
[Claim 18]

A following formula which are following formula (III) and its tautomer (IIIa) :

[Chemical formula 10]

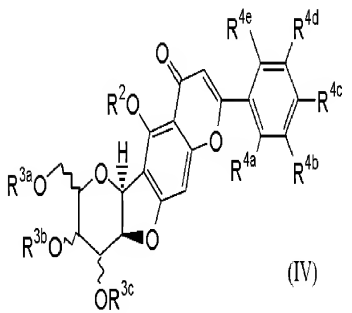


(III)



(IIIa)

Following formula (IV) by coming out and making an acid act to a compound expressed :
[Chemical formula 11]



(IV)

R^{3a}, R^{3b}, and R^{3c} express a protective group of a hydroxyl group among [above-mentioned each formula, R^2 expresses a protective group of a hydrogen atom or a hydroxyl group, and, [R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e}]] which expresses independently an alkyl group of a straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, an alkoxy group of branched chain and a straight chain of the carbon numbers 1-6, or branched chain, an R^5-O-group (R^5 expresses a protective group of a hydroxyl group), or a halogen atom, respectively

A manufacturing method of a compound come out of and expressed.

[Claim 19]

The manufacturing method according to claim 18 on which an acid is made to act to a compound denoted by a formula (IIIa) which are formula (III) whose R^2 is a methyl group, and whose R^{3a}, R^{3b}, and R^{3c} are benzyls, and its tautomer.

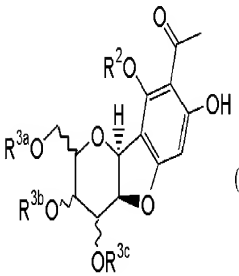
[Claim 20]

It is trimethylsilyl as an acid. The manufacturing method according to claim 18 or 19 on which trifluoro methanesulfonic acid is made to act.

[Claim 21]

Following formula (IV) :

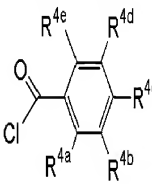
[Chemical formula 12]



(VI)

They are the bottom of existence of a base, and following formula (VII) to a compound come out of and expressed. :

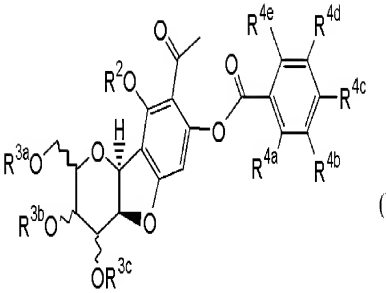
[Chemical formula 13]



(VII)

Come out, a compound expressed is made to react and it is following formula (VIII). :

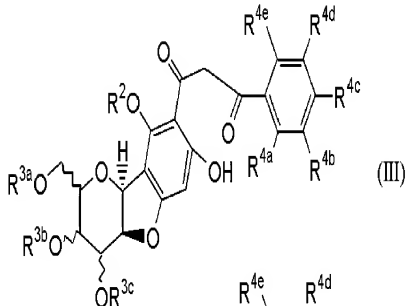
[Chemical formula 14]



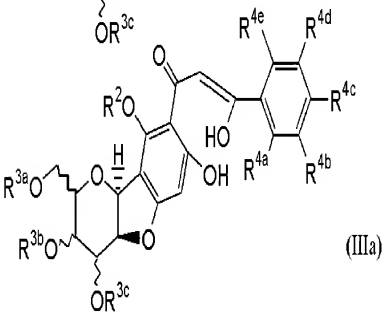
(VIII)

Following formula which are following formula (III) characterized by making a base act after coming out and considering it as the compound expressed, and its tautomer (IIIa) :

[Chemical formula 15]



(III)



(IIIa)

R^{3a}, R^{3b}, and R^{3c} express the protective group of a hydroxyl group among [above-mentioned each formula, R^2 expresses the protective group of a hydrogen atom or a hydroxyl group, and, [R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e}]] which expresses independently the alkyl group of the straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, the alkoxy group of branched chain and the straight chain of the carbon numbers 1-6, or branched chain, an R^5-O-group (R^5 expresses the protective group of a hydroxyl group), or a halogen atom,

respectively

A manufacturing method of a compound come out of and expressed.

[Claim 22]

A compound which is formula (VI) indicated to Claim 21, and is expressed.

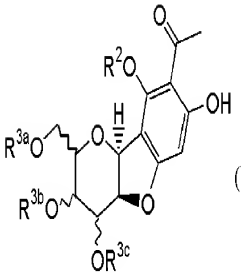
[Claim 23]

A compound which is indicated to Claim 21, whose R^2 formula (VI) sets and is a methyl group and whose R^{3a}, R^{3b}, and R^{3c} are benzyls.

[Claim 24]

Following formula (VI) :

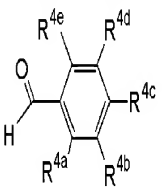
[Chemical formula 16]



(VI)

They are the bottom of existence of a base, and following formula (IX) to a compound come out of and expressed. :

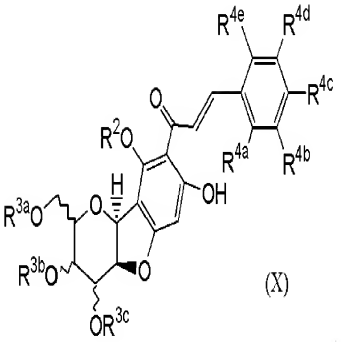
[Chemical formula 17]



(IX)

Come out, a compound expressed is made to react and it is following formula (X). :

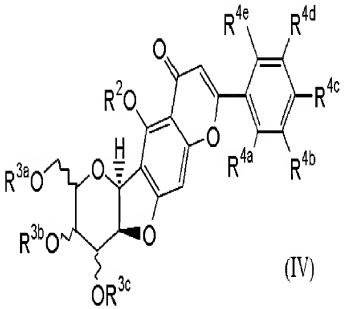
[Chemical formula 18]



(X)

Following formula (IV) characterized by making heating or a base act under existence of an oxidizing agent after coming out and considering it as the compound expressed :

[Chemical formula 19]



(IV)

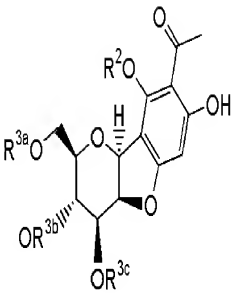
R^{3a}, R^{3b}, and R^{3c} express the protective group of a hydroxyl group among [above-mentioned each formula, R^2 expresses the protective group of a hydrogen atom or a hydroxyl group, and, [R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e}]] which expresses independently the alkyl group of the straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, the alkoxy group of branched chain and the straight chain of the carbon numbers 1-6, or branched chain, an R^5-O-group (R^5 expresses the protective group of a hydroxyl group), or a halogen atom, respectively

A manufacturing method of a compound come out of and expressed.

[Claim 25]

Following formula (XI) :

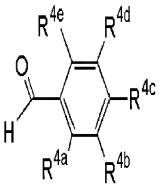
[Chemical formula 20]



(XI)

They are the bottom of existence of a base, and following formula (IX) to the compound come out of and expressed. :

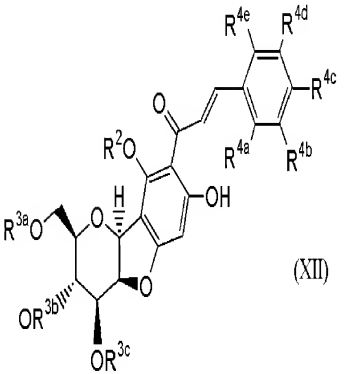
[Chemical formula 21]



(IX)

Come out, the compound expressed is made to react and it is following formula (XII). :

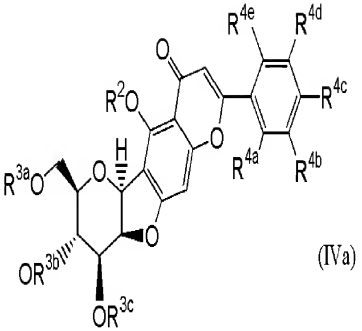
[Chemical formula 22]



(XII)

Following formula characterized by making heating or a base act under existence of an oxidizing agent after coming out and considering it as the compound expressed (IVa) :

[Chemical formula 23]



(IVa)

R^{3a}, R^{3b}, and R^{3c} express the protective group of a hydroxyl group among [above-mentioned each formula, R^2 expresses the protective group of a hydrogen atom or a hydroxyl group, and, [R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e}]] which expresses independently the alkyl group of the straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, the alkoxy group of branched chain and the straight chain of the carbon numbers 1-6, or branched chain, an R^5-O-group (R^5 expresses the protective group of a hydroxyl group), or a halogen atom, respectively

A manufacturing method of a compound come out of and expressed.

[Claim 26]

A manufacturing method which uses iodosobenzene acetate or iodine as an oxidizing agent in a method according to claim 24 or 25.

[Claim 27]

A compound which is the formula (XII) according to claim 25, and is expressed.

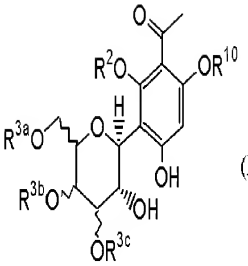
[Claim 28]

A compound whose R^2 is a methyl group in a compound of the formula (XII) according to claim 25 and whose R^{3a}, R^{3b}, and R^{3c} are benzyls.

[Claim 29]

Following formula (XIII) :

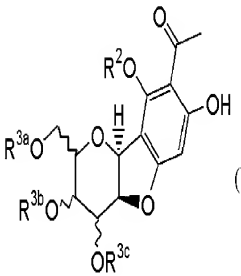
[Chemical formula 24]



(XIII)

Come out and to a compound expressed Inside of $P(R^6)_3$ and an $R^7CON{=}NCOR^7$ {type, R^6 expresses an alkyl group, no substituting, or a substituted phenyl group of a straight chain of the carbon numbers 1-6, or branched chain, R^7 -- group:, [R^8O- or $(R^9)_2N$-[R^8 and R^9] Following formula (VI) making it act that independently,] showing an alkyl group of a straight chain of the carbon numbers 1-6 or branched chain is expressed}, and carrying out deprotection of the R^{10} if required :

[Chemical formula 25]



(VI)

(R^{3a}, R^{3b}, and R^{3c} express the protective group of a hydroxyl group among each above-mentioned formula, R^2 expresses the protective group of a hydrogen atom or a hydroxyl group, and R^{10} expresses the protective group of a hydrogen atom or a hydroxyl group)

A manufacturing method of a compound come out of and expressed.

[Claim 30]

A compound which is the formula (XIII) according to claim 29, and is expressed.

[Claim 31]

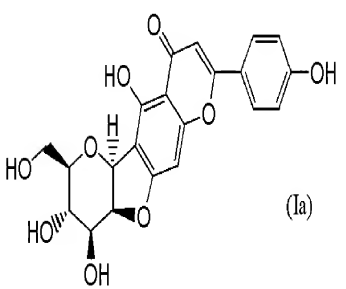
A compound whose R^2 is a methyl group in a compound of formula (XIII) indicated to Claim 29 and whose R^{3a}, R^{3b}, and R^{3c} are benzyls.

[Claim 32]

A medicinal composition which contains a compound of a description, or its salt permitted pharmacologically as an active ingredient in Claims 1, 2, 3 and 4 and any 1 paragraph of 5.

[Claim 33]
A medicinal composition which is one sort or inertness beyond it permitted in galenical pharmacy, and contains a compound given in Claims 1, 2, 3 and 4 and any 1 paragraph of 5, or its salt permitted pharmacologically with a harmless carrier as an active ingredient.
[Claim 34]
The medicinal composition according to claim 32 or 33 used for prevention or a therapy of an allergic disease.
[Claim 35]
The medicinal composition according to claim 34 whose allergic diseases are atopic dermatitis and cutaneous sensitization.
[Claim 36]
The medicinal composition according to claim 32 or 33 used for prevention or a therapy of an inflammatory disease.

[Detailed Description of the Invention]
[0001]
[Field of the Invention]
This invention relates to the new flavone derivative which has anti-inflammatory activity or its salt permitted pharmacologically, those manufacturing methods, and the producing intermediate of those.
[0002]
[Description of the Prior Art]
Until now, much flavone which have anti-inflammatory activity is known. this invention person found out the new flavone derivative which has new and powerful anti-inflammatory activity this time, as a result of having inquired wholeheartedly about the compound which has anti-inflammatory activity. Following formula indicated to the application for patent 2002-194828 which has the anti-inflammatory activity pass the manufacturing process of a multi stage story from the oolong tea-leaves extract by using how to manufacture the new flavone derivative which this invention provides (Ia) :
[0003]
[Chemical formula 26]



(Ia)

It found out that it came out and the compound expressed could be manufactured by a simple method.

[0004]

The new flavone derivative which this invention provides found out that it was very effective to the therapy of an antiallergic action especially atopic dermatitis, and cutaneous sensitization.

[0005]

[Problem to be solved by the invention]

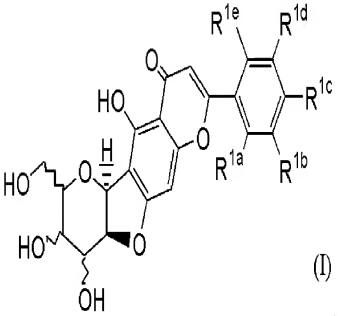
Therefore, this invention has anti-inflammatory activity and makes it a technical problem to provide a new flavone derivative or its salt permitted pharmacologically effective in prevention or the therapy of an antiallergic agent especially atopic dermatitis, and cutaneous sensitization, those manufacturing methods, and the producing intermediate of those.

[0006]

[Means for solving problem]

This invention for solving this technical problem is following formula (I). :

[Chemical formula 27]



(I)

[0007]

(R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} express independently the alkyl group or halogen atom of the straight chain of a hydrogen atom, a hydroxyl group, and the carbon numbers 1-6, the alkoxy group of branched chain and the straight chain of the carbon numbers 1-6, or branched chain among a formula, respectively)

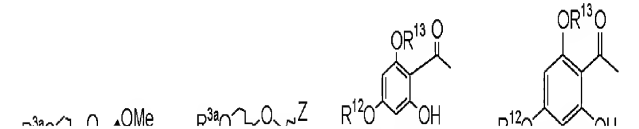
It comes out and the compound expressed and its salt permitted pharmacologically are provided.

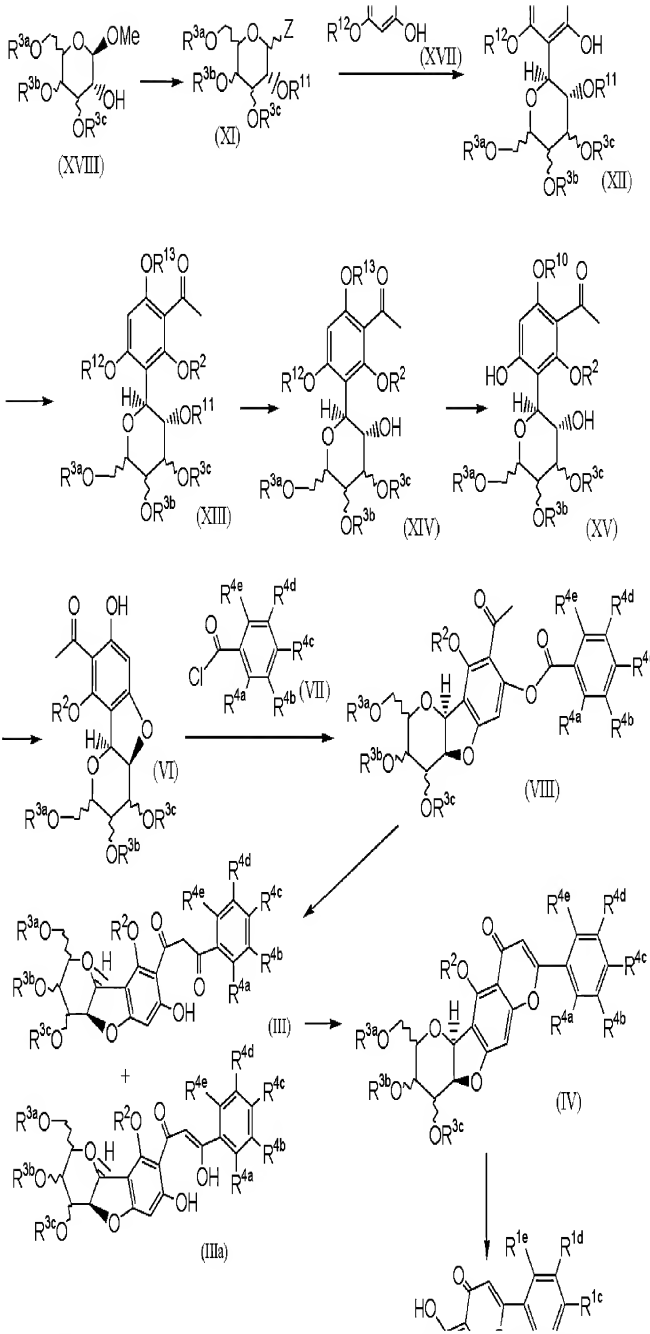
The manufacturing method of the flavone derivative shown by this formula (I) is provided.

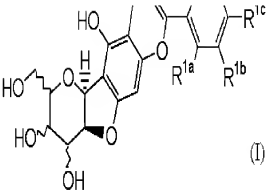
Specifically, the manufacturing method can be expressed by the method shown in the following chemical formula.

[0008]

[Chemical formula 28]





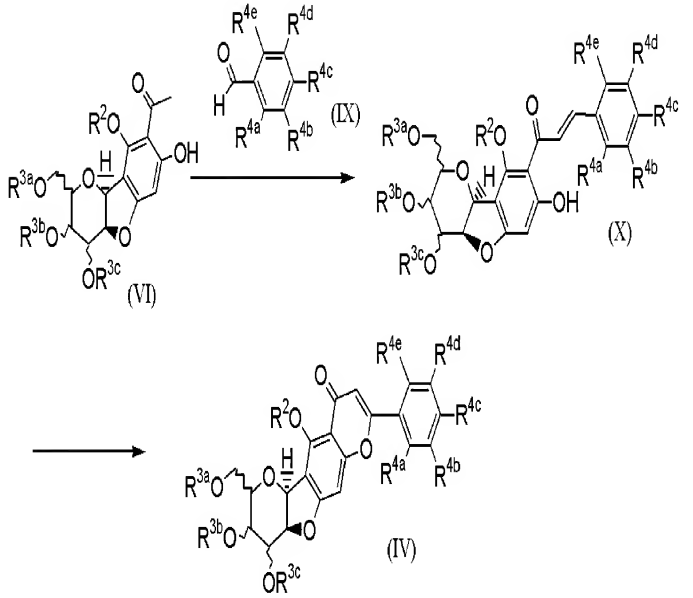


(I)

[0009]

There is also a method of resulting [from compound (VI) besides the above-mentioned method] in compound (IV) through compound (X).

[Chemical formula 29]



[0010]

(Refer to the definition which carries out a postscript for the definition of each substituent in the above-mentioned chemical formula)

That is, this invention provides the new flavone derivative denoted by formula (I) shown in the above-mentioned chemical formula, its manufacturing method and the manufacturing method of the intermediate, and the intermediate concerned.

[0011]

[Mode for carrying out the invention]

Hereafter, this invention is explained in detail based on the above-mentioned reaction formula.

[0012]

It is a sign so that clearly for a person skilled in the art, unless it refuses especially in this invention. :

[Chemical formula 30]

It means having combined with ** and the other side of space, i.e., alpha-arrangement, and is a sign. :

[Chemical formula 31]

It means having combined with the ** and this side side of space, i.e., beta-arrangement, and is a sign. :

[Chemical formula 32]

It expresses that they are **, alpha-, or beta-arrangement or those mixtures.

[0013]

The compound denoted by formula (I) or formula (II) or its salt permitted pharmacologically is convertible for solvate by a publicly known method. As suitable solvate, the solvate of water and the solvents (for example, ethanol etc.) of an alcohol system is raised, for example. The method of recrystallizing as a method of changing into solvate from the water or the organic solvent indicated, for example to pharmaceutics (Hitoshi Shiozaki, the 150th page of Hirokawa Publishing (1989) edited by the Kimura ******) is raised.

[0014]

[protective group / which is denoted by substituent R^2, R^{3a}, R^{3b}, R^{3c}, R^5, and R^{10} here] It is a functional group which can be introduced under a specific condition to a hydroxyl group, and when it is necessary to react under a specific condition but to change into a hydroxyl group, the functional group which can be used as a hydroxyl group is said by carrying out deprotection under a certain condition. [as such R^2, R^{3a}, R^{3b}, R^{3c}, R^5, and R^{10}] An aryl methyl group; allyl group; methyl group like benzyl and p-nitrobenzyl group; An acetyl group, Acyl groups, such as benzoyl; silyl group; t-butoxycarbonyl groups, such as t-butyldimethylsilyl group and t-butylphenylsilyl group, and the group which is joined to a hydroxyl group like a benzyloxycarbonyl group, and forms carbo NATO can be used.

[0015]

The introduction is known well, for example, if benzyl is mentioned as an example, it can be introduced by making a benzyl bromide or benzyl chloride act under existence of bases, such as NaH and K_2CO_3, to the compound which has a hydroxyl group.

[0016]

The deprotection Ester; benzene, such as alcohols; ethyl acetate, such as ethanol or methanol, Aromatic

hydrocarbon, such as toluene; Organic acid ****, such as ether; acetic acid, such as diethylether and tetrahydrofuran, the inside of the solvent of these arbitrary combination, It can carry out by agitating under catalyst existence, such as Pd-carbon, $Pd(OH)_2$, and Pd black, and hydrogen gas atmosphere. Deprotection can be carried out also under acid conditions, such as BCl_3, $AlCl_3$, and HBr.

[0017]

Deprotection of the protective group shown above can be carried out by using transition metal complexes, such as basic condition, reductive condition, and acidity conditions or Bu_4NF, and Pd, etc. Although each combination changes with the combination of the protective group to be used, or combination which need deprotection, [combination] For example, when benzyl and a methyl group are used as a protective group, respectively. If Pd-carbon existence sewage matter gas is made to act, deprotection only of the benzyl can be carried out, and when the methyl group is used as a protective group of a phenolic hydroxyl group by making BCl_3 act, deprotection of benzyl and the methyl group will be carried out simultaneously. When the methyl group is used as a protective group of a phenolic hydroxyl group by making $AlBr_3$ act among acetonitrile, even if other hydroxyl groups are protected by benzyl, deprotection only of the methyl group can be carried out alternatively.

[0018]

Besides having described above, if it is introduction and a group which can carry out deprotection easily and alternatively, it will not be limited in particular. For example, [conditions / selection of a protective group, combination, and / deprotection] T. . [W. Greene, P. G.M. Wuts, : "Protective Groups in Organic Synthesis 2nd. Ed., John Wiley & Sons, and Inc. New York 1991", etc.] It can be referred to.

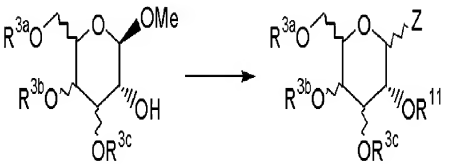
[0019]

Each manufacturing process of this invention is explained in detail below.

[0020]

The first process :

[Chemical formula 33]



(XVIII) (XI)

(R^{3a}, R^{3b}, R^{3c}, and R^{11} express the protective group of a hydroxyl group among a formula, and Z expresses imidate or a fluorine atom)

[0021]

This first process protected 2 place hydroxyl group of methyl pyranoside R^{3a}, After introducing the protective group which can carry out deprotection according to conditions different, respectively from R^{3b} and R^{3c}, they are a hydrolysis of methyl pyranoside, and the process of subsequently to the 1st place introducing imidate or a fluorine atom. Compound (XVIII) which is a starting material R^{3a}, R^{3b}, When R^{3c} is benzyl, it can compound by the method [J. Amer. Chem. Soc., Vol.111, and 6661] (1992) of Danishefsky and others. Also when other protective groups are used, the method according to it or this can be made into a raw material, and can be compounded.

[0022]

[as substituent R^{3a}, R^{3b}, or R^{3c}] Ether type protective group;t-butyldimethylsilyl groups, such as benzyl and an allyl group, A silyl ether type protective group like t-butylphenylsilyl group; Are acyl mold protective groups, such as an acetyl group and benzoyl, and, [as R^{11}] Silyl ether type protective groups, such as ether type protective group [, such as p-nitrobenzyl group, benzyl, and an allyl group,]; or t-butyldimethylsilyl group, and t-butylphenylsilyl group, can be raised.

[0023]

In this case, the same protective group is not simultaneously used for R^{3a}, R^{3b}, R^{3c}, and R^{11}. When R^{3a}, R^{3b}, and R^{3c} are benzyls and R^{11} is p-nitrobenzyl group, To the compound of formula (XVIII), aromatic hydrocarbon; ether, such as halogenated hydrocarbon; benzene, such as a methylene chloride and chloroform, 0-80 ** of ether, such as tetrahydrofuran and dioxane, etc. are room temperature -40 ** preferably under existence of silver oxide or silver methanesulfonate (I) among a methylene chloride desirably, chloridation p-nitrobenzyl or bromination -- a 2-O-p-nitrobenzyl pyranoside derivative can obtain by making p-nitrobenzyl act.

[0024]

as opposed to the obtained sugar derivative -- the bottom of acid condition, i.e., inside of dilute-sulfuric-acid in acetic acid, or dilute sulfuric acid, and room temperature - 150 ** of 1-hydroxy pyranose derivatives can be obtained by heating at 90-120 ** preferably. This Under existence of inorganic bases, such as an organic base still like diazabicycloundecen (DBU) or Cs_2CO_3, Although ether, such as aromatic hydrocarbon; ether, such as halogenated hydrocarbon; benzene, such as a methylene chloride and chloroform, tetrahydrofuran, and dioxane, or two or more sorts of these mixtures can be used as a solvent, [trichloroacetonitrile] Desirably, 0-60 ** compound (XI) [Z:-O(C=NH)-CCl_3] can be obtained by making it react at a room temperature preferably among a methylene chloride.

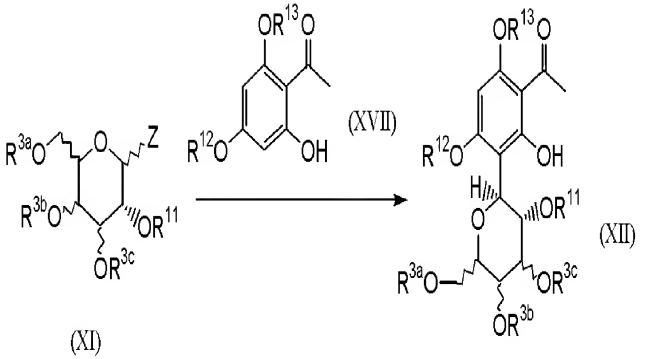
[0025]

Or the 1-hydroxy pyranose derivative shown above is received, It is [in / inside of halogenated hydrocarbon, such as a methylene chloride and chloroform, or these mixed solvents / -78 **--40 **] sulfas (dimethylamine). . [make / trifluoride / to act] After deriving a 1-hydroxy pyranose derivative to 1-acetyl object by the usual method, compound (XI)[Z:F] can be obtained also by making a pyridine- HF complex act.

[0026]

The 2nd process :

[Chemical formula 34]



[0027]

the 2nd process receives pyranose derivative (XI) -- 2', 4', and 6' -- among a - trihydroxy acetophenone derivative (XVII)[type, [R^{12} and R^{13}] If it does not react and what is necessary is not to check a reaction, and just to give an example in this reaction, Ether, such as benzyl; when Lewis acid carries out existence bottom operating of] which can use silyl ether, such as t-butylphenylsilyl group, etc., it is a reaction which forms C-glycoside alternatively.

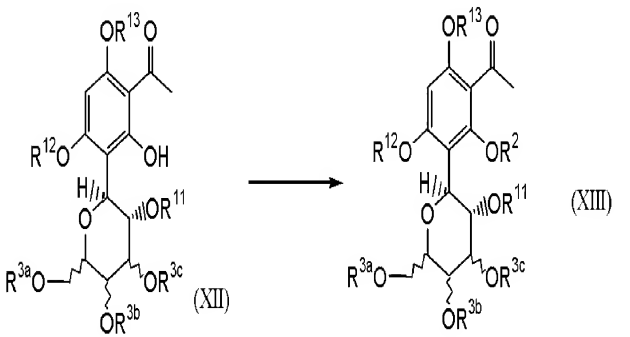
[0028]

compound (XVII) -preferably 78 ** - 60 ** in -40 ** - a room temperature, BF_3 diethylether complex, trimethylsilyl Compound (XII) can be obtained by making reaction accelerators, such as trifluoro methanesulfonic acid (TMSOTf) and Cp_2HfCl_2-$AgClO_4$, act.

[0029]

The 3rd process :

[Chemical formula 35]



[0030]

The 3rd process is a process of protecting the phenolic hydroxyl group of compound (XII). R^{11}, R^{12} which are the protective groups of other hydroxyl groups as a protective group, Be [what is necessary / just although it does not react in the deprotection process of the protective group of R^{13}], with the kind of protective group of R^{3a}, R^{3b}, R^{3c}, R^{11}, R^{12}, and R^{13}, For example, acetal type protective groups, such as ether nature protective group; methylthio methyl groups, such as a methyl group, an allyl group, and a vinyl group, and a trimethylsilyl methoxymethyl group; acyl mold protective groups, such as an acetyl group and benzoyl, etc. can be used.

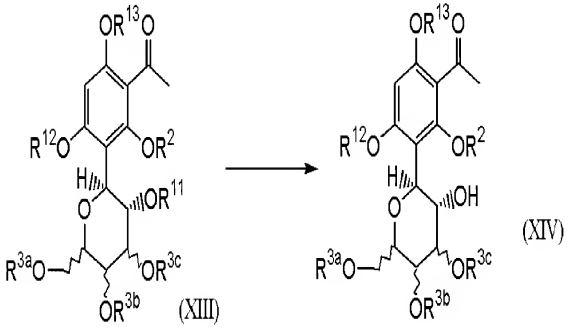
[0031]

For example, R^{3a}, R^{3b}, R^{3c}, R^{12}, and R^{13} are benzyls, and when R^{11} is p-nitrobenzyl group, a methyl group can be chosen as R^2, for example. Although the introducing method of a protective group should just apply what is used with the usual manufacturing method, when introducing a methyl group, [the introducing method] For example, ketone [, such as acetone and methyl ethyl ketone,]; or the amide like dimethylformamide is used as a solvent, It can obtain by making methylation agents, such as MeI and Me_2SO_4, act at -20 ** thru/or 80 ** under existence of organic bases, such as inorganic bases, such as K_2CO_3, Na_2CO_3, and NaH, or diisopropylethylamine. If the obtained object is required, recrystallization and chromatography can refine it.

[0032]

The 4th process :

[Chemical formula 36]



[0033]

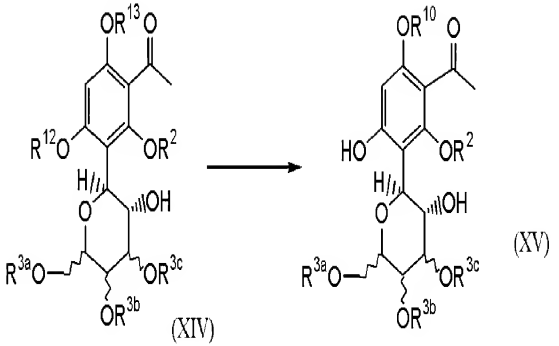
The 4th process is a deprotection process of the protective group of R^{11} which is a hydroxyl group of the 2nd place of pyranose. As deprotection conditions, the protective group of R^{3a} which is a protective group of a hydroxyl group, R^{3b}, R^{3c}, R^{12}, and R^{13} should not just react in this deprotection process. For example, R^{3a}, R^{3b}, R^{3c}, R^{12}, When R^{13} is benzyl, R^2 is a methyl group and R^{11} is p-nitrobenzyl group, Purpose compound (XIV) can be obtained for an ammonium chloride aqueous solution among the mixed solvent of alcohols, such as methanol, ethanol, and isopropanol, and water under existence of the indium powder of an overlarge a room temperature thru/or by making 100 ** react at 60 ** thru/or 90 ** preferably. If the obtained object is required,

recrystallization and chromatography can refine it.

[0034]

The 5th process :

[Chemical formula 37]



(XIV) (XV)

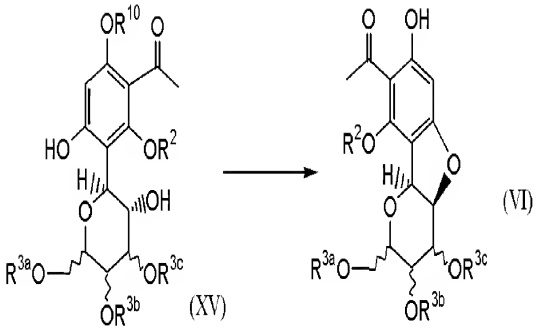
[0035]

The 5th process is a deprotection process of R^{12} which is a protective group of a hydroxyl group. As deprotection conditions, R^2 which is a protective group of a hydroxyl group, R^{3a}, R^{3b}, and R^{3c} should not just react in these deprotection processes. Even if deprotection of the protective group R^{13} is carried out in this process, it does not need to react. For example, when R^{3a}, R^{3b}, R^{3c}, R^{12}, and R^{13} are benzyls and R^2 is a methyl group. Ether like tetrahydrofuran is used for Pd-carbon catalyst as a solvent under hydrogen gas atmosphere, distilling off under a reduced pressure of a solvent, after agitating this under ordinary pressure in a room temperature preferably and filtering the catalyst after the completion of a reaction, 0 ** thru/or a room temperature, and -- purpose compound (XV) -- it can obtain [R^{10} expresses a hydrogen atom or a protective group among a formula]. In this case, deprotection also of the R^{13} is carried out and R^{10} serves as a hydrogen atom. If the obtained object is required, recrystallization and chromatography can refine it.

[0036]

The 6th process :

[Chemical formula 38]



(XV) (VI)

[0037]

The 6th process is the deprotection reaction, when the dehydrating condensation reaction process accompanied by solid inversion and R^{10} of a hydroxyl group of the 2nd place of sugar the 2nd place of the sugar of a hydroxyl group and a phenolic hydroxyl group are a protective group of a hydroxyl group. Substituent R^2, R^{3a}, R^{3b}, R^{3c}, Be [what is necessary / just although R^{10} does not react in this reaction], a hydrogen atom etc. can be raised as a methyl group and R^{10} as benzyl and R^2 as R^{3a}, R^{3b}, and R^{3c}, for example.

[0038]

A reaction can be performed by using the Mitsunobu reaction, for example. Specifically Under existence of trialkylphosphine, such as aryl phosphine [, such as triphenyl phosphine,]; or tributyl phosphine, The azo compound used for the usual Mitsunobu reactions, such as diethyl AZOJI carboxylate or tetramethyl azodicarboxamide, benzene, Aromatic hydrocarbon, such as toluene; among ether, such as halogenated hydrocarbon; diethylether, such as a methylene chloride and chloroform, and tetrahydrofuran, there is no -40 ** and 40 ** can be preferably obtained 1 hour thru/or by making it react for 48 hours at a room temperature.

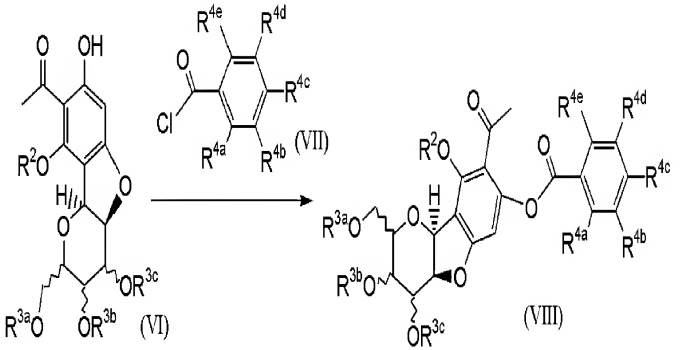
[0039]

When R^{10} is a hydrogen atom, object (VI) is obtained by performing after-treatment usual [after the completion of a reaction]. If object (VI) is required, recrystallization and chromatography can refine it. When R^{10} is a protective group of a hydroxyl group, deprotection of protective group R^{10} is performed further. If obtained compound (VI) is required, recrystallization and chromatography can refine it.

[0040]

The 7th process :

[Chemical formula 39]



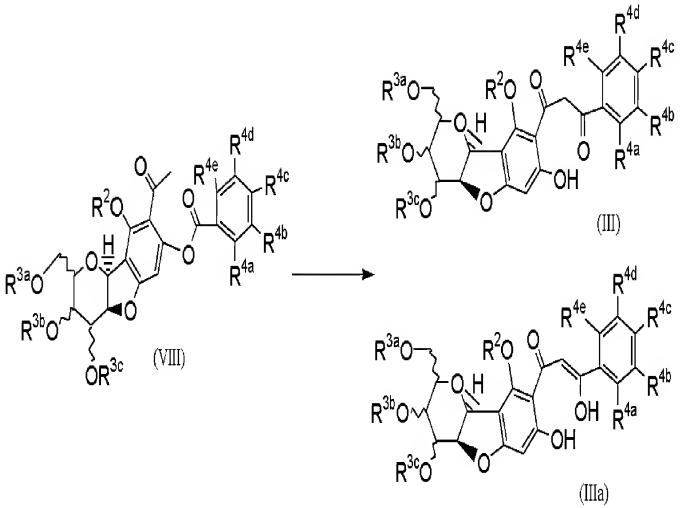
[0041]

R^2 which is a protective group in this process, R^{3a}, R^{3b}, Be [what is necessary / just although R^{3c} does not react in this reaction], a methyl group etc. can be raised as R^2 and it can raise benzyl etc. as R^{3a}, R^{3b}, and R^{3c}, for example. A reaction to compound (VI) specifically Under existence of bases, such as 4-dimethylaminopyridine or pyridine, Halogenated hydrocarbon, such as aromatic hydrocarbon; methylene chlorides, such as benzene and toluene, and chloroform; Diethylether, The inside of ether, such as tetrahydrofuran, or these combination mixed solvents, [among 1 equivalent amount thru/or 2 equivalent amount, and the desirable compound (VII)[type of 1.2 equivalent amount] [R^{4a} and R^{4b}, R^{4c}, R^{4d}, and R^{4e}] There is no -20 **, 10 minutes of 40 ** cannot be preferably found in a room temperature, and] synonymous with the definition of Claim 6 is made to act for 24 hours. If the compound obtained by performing after-treatment usual [after the completion of a reaction] is required, it can be refined by methods usually used, such as recrystallization and chromatography, and can obtain object (VIII).

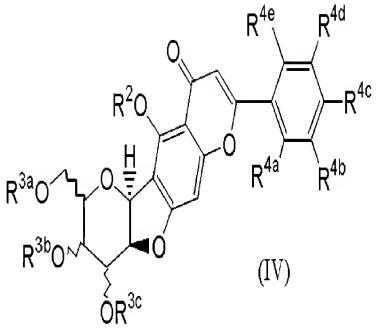
[0042]

The 8th process :

[Chemical formula 40]

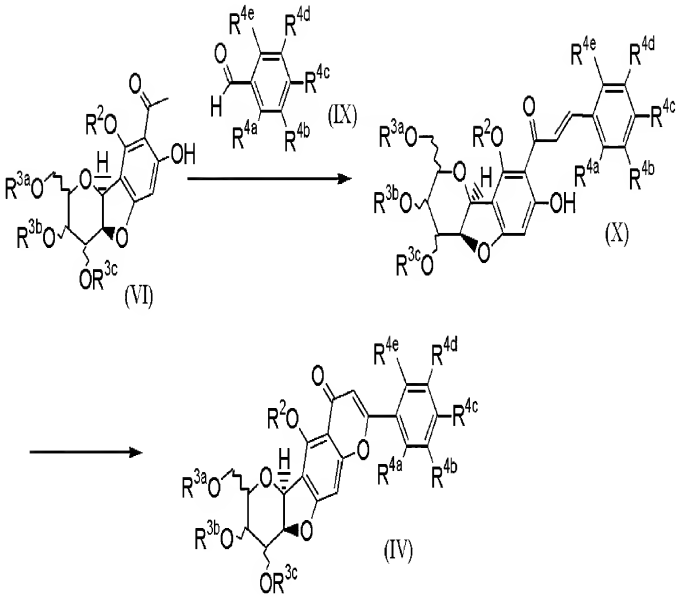


[0043]
The 8th process is a conversion process of being compound (III) from compound (VIII), and its tautomer (IIIa). Be [what is necessary / just although substituent R^2 R^{3a}, R^{3b}, and R^{3c} do not react in this reaction], benzyl etc. can be raised as R^{3a}, R^{3b}, and R^{3c} and they can raise a methyl group etc. as R^2, for example. Substituent R^{4a}, R^{4b}, and R^{4c}, R^{4d}, and R^{4e} are synonymous with the definition of Claim 6.
[0044]
A reaction to compound (VIII) specifically Aromatic hydrocarbon; diethylether, such as benzene and toluene, Ether, such as tetrahydrofuran; The inside of hexane, pentane, or these combination mixed solvents, LDA (lithium diisopropylamide) -- 1 equivalent amount thru/or 15 equivalent amount -- desirable -- 2 equivalent amount thru/or 10 equivalent amount -78 ** -- or 40 ** of objects can be preferably obtained 10 minutes thru/or by making it react for 2 hours at -20 ** thru/or a room temperature. If the compound obtained by performing after-treatment usual [after the completion of a reaction] is required, it can be refined by methods usually used, such as recrystallization and chromatography, and can obtain object (III) and its tautomer (IIIa).
[0045]
The 9th process :
[Chemical formula 41]

(III) + (IIIa) → 

(IV)

[0046]
The 9th process is a process of building a flavone skeleton from compound (III) and its tautomer (IIIa). In this reaction, [substituent R^2, R^{3a}, R^{3b}, and R^{3c}] That what is necessary is just what does not react and does not check a reaction, [[substituent R^{4a}, R^{4b}, R^{4c}, R^{4d} and R^{4e}]] synonymous with the definition of Claim 6 can raise benzyl etc. as R^{3a}, R^{3b}, and R^{3c}, and can raise a methyl group etc. as R^2, for example.
[0047]
A reaction specifically receives compound (III) and its tautomer (IIIa), Halogenated hydrocarbon, such as a methylene chloride and chloroform; Preferably in [there are not inside of ether /, such as diethylether and tetrahydrofuran, /; or these combination mixed solvents and -20 **, and] a room temperature 40 **, 1 thru/or Lewis acid of 3 equivalent amount, for example, trimethylsilyl, Object (IV) can be obtained for a trifluoromethanesulfonate or a hydrochloric acid aqueous solution 10 minutes thru/or by making it act for 24 hours. If the obtained object is required, recrystallization and chromatography can refine it.
[0048]
As explained above, can also perform gradually the 7th process, the 8th process, and the 9th process of having explained here, but. To compound (VI), aromatic hydrocarbon; methylene chlorides, such as benzene and toluene, Halogenated hydrocarbon, such as chloroform; The inside of ether [, such as diethylether and tetrahydrofuran,]; or these combination mixed solvents, Compound (IV) can be obtained also by making compound (VII) act at a room temperature thru/or 120 ** under existence of diazabicycloundecen (DBU) of 1 equivalent amount thru/or 4 equivalent amount.
[0049]
Unlike the method described above, manufacturing methods of compound (IV) also include the following method.
[Chemical formula 42]



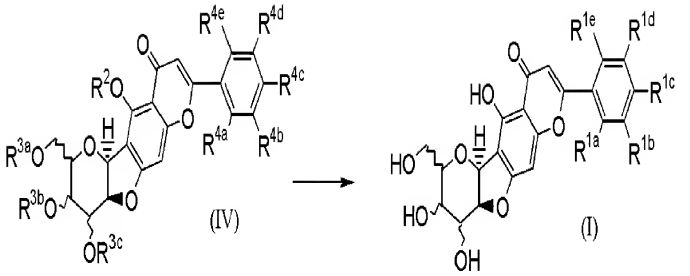
[0050]

Namely, the inside of a compound (VI)[type, substituent R^2, R^{3a}, [R^{3b}, R^{3c}, R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e}] The inside of the solvent mixed with water, such as dimethyl sulfoxide and dioxane, to] synonymous with the definition of Claim 6, If required after making compound (IX) act at 0 ** thru/or 80 ** and considering it as compound (X) under existence of the base of 1 equivalent amount thru/or 10 equivalent amount, for example, KOH, and a NaOH aqueous solution, Compound (IV) can be obtained by refining this by the usual method and heating under an acid condition to compound (X) further. For example, iodine or DDQ (2,3-dichloro-5,6-dicyano 1, 4-benzoquinone) can be used as an oxidizing agent. Compound (IV) can also be obtained to compound (X) by making bases, such as bottom methanol Nakamizu potassium oxide of iodosobenzene acetate existence, act at a room temperature.

[0051]

The 10th process :

[Chemical formula 43]



[0052]

The 10th process is a deprotection process of the protective group of compound (IV). Be [what is necessary / just although substituent R^2 R^{3a} and R^{3b} and R^{3c} can be used as a protective group in a process until now], specifically, Benzyl, an acetyl group, etc. can be raised as R^{3a}, R^{3b}, and R^{3c}, and a methyl group, an acetyl group, etc. can be raised as R^2. Substituent R^{4a}, R^{4b}, and R^{4c}, R^{4d}, and R^{4e} are synonymous with the definition of Claim 6.

[0053]

The process of deprotection should just be a method which changes these protective groups into a hydroxyl group, and does not cause decomposition of compound (IV) and compound (I). It is obvious if it is a person skilled in the art about selection of those methods. [conditions / of deprotection] T. . [W. Greene, P. G. M. Wuts, : "Protective Groups in Organic Synthesis 2nd. Ed., John Wiley & Sons, and Inc. New York 1991", etc.] It can be referred to.

[0054]

For example, compound (IV) which is benzyl as substituent R^{3a}, R^{3b}, and R^{3c}, and is a methyl group as R^2 is received, Aromatic hydrocarbon, such as benzene and toluene; The inside of halogenated hydrocarbon [, such as a methylene chloride and chloroform,]; or these combination mixed solvents, There is no -20 ** and preferably BCl_3 40 **, [0 ** thru/or a room temperature] 10 minutes -- or -- making it act for 5 hours -- after that-20 ** -- or preferably 40 **, 10 minutes in methanol thru/or after agitating for 2 hours, [0 ** thru/or a room temperature] The reaction solution obtained by agitating among the mixed solvent of churning of acetic acid-water among a mixed solvent or methanol, and a hydrochloric acid aqueous solution can be obtained by performing the usual after-treatment. If this object is required, it can be refined by methods usually used, such as recrystallization and chromatography.

[0055]

When substituent R^2, R^{3a}, R^{3b}, and R^{3c} are acetyl groups, Ether, such as tetrahydrofuran; compound (I) can be obtained by making bases, such as sodium hydroxide and potassium hydroxide, act among alcohols, such as ethanol and methanol. It is not necessary to necessarily perform this process in one step, it can be divided into several steps, and can also be performed. If substituent R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e} have some which have a protective group of a hydroxyl group in the group, Compound (I) can be obtained by performing the process of carrying out deprotection of that protective group separately, among the deprotection process of this protective

group.

[0056]

It aims at simplification of a purification process, or improvement in a yield as the method of deprotection, A deprotection process can also be performed after introducing another protective group into the hydroxyl group which carries out deprotection of the part and generates altogether the protective group first shown by substituent R^2, R^{3a}, R^{3b}, and R^{3c}. As a protective group newly introduced at this time, acyl group;t-butyldimethylsilyl groups, such as an acetyl group and benzoyl, Silyl groups, such as t-butylphenylsilyl group; the group which is joined to a hydroxyl group like a t-butoxycarbonyl group and a benzoyloxy carbonyl group, and forms carbo NATO can be used. Although the method of the deprotection at the time of introducing these protective groups is obvious to a person skilled in the art, For example, T. . [W. Greene, P. G. M. Wuts, : "Protective Groups in Organic Synthesis 2nd. Ed., John Wiley & Sons, and Inc. New York 1991", etc.] It can be referred to. For example, when R^2 is a methyl group and uses benzyl as R^{3a}, R^{3b}, and R^{3c}. After protecting the hydroxyl group generated after carrying out deprotection of R^2, R^{3a}, R^{3b}, and the R^{3c} by an acetyl group, deprotection of all the protective groups can be again carried out for this simultaneously.

[0057]

[the flavone derivative which this invention provides, or its salt permitted pharmacologically] Since an antiallergic action is shown and the oedema-auricular formation depressant action induced by especially TNCB (2,4,6-trinitro 1-chlorobenzene) is shown, it is an effective compound especially to the therapy of atopic dermatitis and cutaneous sensitization as an antiallergic agent.

[0058]

In applying the flavone derivative which this invention provides, or its salt permitted pharmacologically to the therapy of an antiallergic agent especially atopic dermatitis, and cutaneous sensitization, For example, a flavone derivative or its salt permitted pharmacologically can be diluted with remaining as it is or water, or it can pharmaceutical-preparation-ize with the publicly known carrier for physic, and a medicine can be orally prescribed for the patient. The form in particular of the pharmaceutical preparation is not restricted, but can be prescribed for the patient as oral solid preparations, such as a tablet, a capsule, a granule, powder, subtle granules, and trochiscus.

[0059]

Various kinds of excipients [in / again / for various kinds of excipients in solid preparations, lubricant, a binder, disintegrator, etc. which are permitted in galenical pharmacy as a carrier for physic used for pharmaceutical preparation-ization / liquid preparations], a suspending agent, a binder, etc. can be raised. Additives, such as antiseptics, an anti-oxidant, a coloring agent, and a sweetening agent, can also be used if needed.

[0060]

As an excipient, can raise lactose, white soft sugar, D-mannitol, a starch, crystalline cellulose, a character silicic acid anhydride, etc., and, for example, [as lubricant] For example, stearic acid, magnesium stearate, calcium stearate, a talc, colloidal silica, etc. can be raised. As a binder, crystalline cellulose, white soft sugar, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinyl pyrrolidone, etc. can be raised. Furthermore as disintegrator, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, sodium citrate, sodium carbonate, etc. can be raised, for example.

[0061]

As a medium used for liquids and solutions, they are raised by purified water, an alcohol, propylene glycol, etc., for example, and, [as a suspending agent] For example, stearic acid ethanolamine, sodium lauryl sulfate, Lauryl aminopropionic acid, lecithin, a benzalkonium chloride, benzethonium chloride, Surface active agents, such as glyceryl monostearate, and also polyvinyl alcohol, Hydrophilic high molecular compounds, such as polyvinyl pyrrolidone, carboxymethylcellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, and hydroxypropylcellulose, etc. can be raised.

[0062]

As antiseptics, p-hydroxybenzoate esters, such as methylparaben and ethylparaben, chlorobutanol, benzyl alcohol, etc. can be raised, and ascorbic acid etc. can be raised as an anti-oxidant.

[0063]

[the dose in the case of using the flavone derivative which this invention provides, or its salt permitted pharmacologically as a treating agent of an antiallergic agent especially atopic dermatitis, and cutaneous sensitization] Although it cannot generally limit according to the kind of a patient's age, weight, and disease, its severity, and a route of administration, generally it is day one to three administration per, and is about 0.001-100mg/kg per 1 treatment.

[0064]

[Working example]

This invention is not limited by these embodiments although an embodiment etc. explain this invention still in detail below.

The numerals used in the following embodiments have a following meaning.

Bn : benzyl

pNB:p-nitrobenzyl group

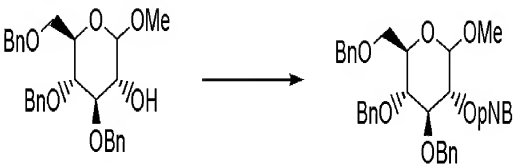
Me : methyl group

Ac : acetyl group

[0065]

Embodiment 1: Manufacture of methyl 3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl D-glucopyranoside

[Chemical formula 44]



[0066]

[the methylene chloride (20 ml) solution of methyl 3,4,5-tri-O-benzyl-D-glucopyranoside (1.35g)] Silver methanesulfonate (990 mg), 2,4,6-collidine (670microl), and p-nitrobenzyl bromide (880 mg) were added under the room temperature, and were agitated for 6 hours. Silver methanesulfonate (990 mg), 2, 4,6-collidine (500microl), and p-nitrobenzyl bromide (470 mg) were added to this reaction solution under the room temperature, and it agitated all night. The obtained filtrate was diluted with ethyl acetate after filtering the

produced insoluble matter. After a saturated potassium bisulfate aqueous solution, saturation brine, saturated sodium bicarbonate water, and saturation brine washed the organic layer one by one, it dried with anhydrous sodium sulfate. Flash chromatography refined the residue obtained by distilling off under a reduced pressure of a solvent, and the mark compound (1.044g) was obtained.

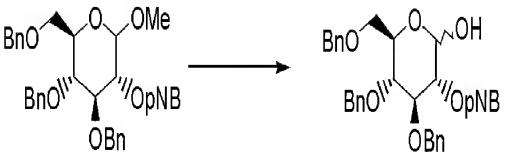
[0067]

NMR. ($CDCl_3$) :. 3.35-3.80(m,6H), 3.54(s,3H), 4.28(d,1H,J=8Hz), 4.5-4.65(m,3H), 4.75-4.84(m,4H), 4.97 (d,1H,J=3Hz),7. 1-7.2 (m, 2H), 7.2-7.4 (m, 13H), 7.43 (d, 2H, J= 8.5 Hz), 8.09 (d, 2H, J= 8.5 Hz).

[0068]

Embodiment 2: Manufacture of 3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl D-glucopyranose

[Chemical formula 45]



[0069]

After carrying out heating flowing back of acetic acid (28 ml) of methyl 3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl D-glucopyranoside (2.6g), and the 2M H_2SO_4 (4 ml) mixed solution for 20 minutes, It opened in the mixture of K_2CO_3 (1.4g) and ice water, and ethyl acetate extracted. The organic layer was dried with anhydrous sodium sulfate after washing one by one with water and saturated sodium bicarbonate water. After carrying out reduced pressure distilling off of the solvent, flash chromatography refined and the mark compound 1.35g was obtained.

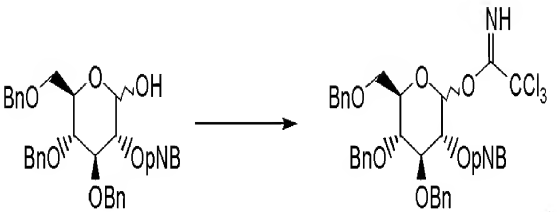
[0070]

NMR($CDCl_3$): 2.83(d,0.5H,J=2.6Hz), 3.3-3.4(m,0.5H), 3.5-3.8(m,4H), 3.95-4.10(m,1.5H), 4.45-4.65(m,3H), 4.7-4.9(m, 5H), 5.0(d,0.5H,J=8.8Hz), 5.3-5.4(m,0.5H), 7.1-7.2(m,2H), 7.2-7.4(m,13H), 7.45(d,2H,J=8.5Hz), 8.05-8.15(m,2H).

[0071]

Embodiment 3: Manufacture of 3,4,5-tri-O-benzyl-1-O-(2,2,2-trichloroethanimidoyl)-2-O-p-nitrobenzyl D-glucopyranose

[Chemical formula 46]



[0072]

To the methylene chloride solution (2 ml) of 3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl D-glucopyranose (130 mg), Cs_2CO_3 (5 mg) and trichloroacetonitrile (0.22 ml) were added at the room temperature, and were agitated for 30 minutes to it. Flash column chromatography refined then and 116 mg of mark compounds were obtained as a mixture of alpha object and beta object.

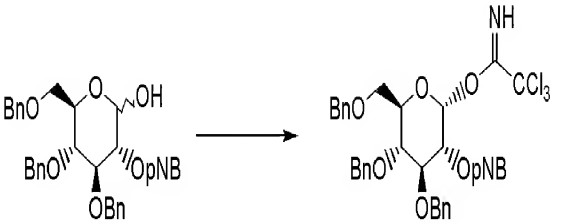
[0073]

NMR. ($CDCl_3$) : 3.6-3.85(m,5H), 3.95-4.1(m,1H), 4.45-5.0(m,8H), 5.79(d,0.5H,J=7.5Hz), 6.57(d,0.5H, J=3.4Hz), 7.1-7.2(m, 2H, 7.2-7.35(m,13H), 7.35-7.45(m,2H), 8.05-8.15(m,2H), 8.55(s,0.5H), 8.71(s,0.5H).

[0074]

Embodiment 4:3,4,5 - Manufacture of tri-O-benzyl-1-O-(2,2,2-trichloroethanimidoyl)-2-O-p-nitrobenzyl alpha-D-glucopyranose

[Chemical formula 47]



[0075]

To the methylene chloride solution (2 ml) of 3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl D-glucopyranose (130 mg), diazabicycloundecen (14microl) and trichloroacetonitrile (0.22 ml) were added at the room temperature, and were agitated for 10 minutes to it. Flash column chromatography refined then and 110 mg of mark compounds were obtained.

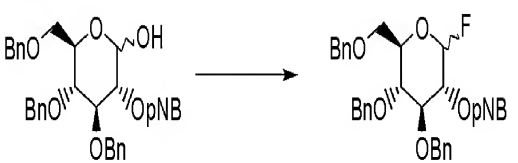
[0076]

NMR. ($CDCl_3$) :. 3.65-3.85(m,4H), 3.95-4.1(m,2H), 4.45-4.65(m,3H), 4.7-4.9(m,5H), 6.57(d,1H,J=3.4Hz), 7.1-7.2(m,2H), 7. 2-7.35 (m, 13H), 7.41(d,2H,J=8.6Hz), 8.11(d,2H,J=8.6Hz), 8.55(s,1H).

[0077]

Embodiment 5: 3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl D-glucopyranosyl Process of a fluoride

[Chemical formula 48]



[0078]

To the methylene chloride solution (1 ml) of 3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl D-glucopyranose (100 mg), it is diethylamino sulfas at -78 **. Trifluoride (34microl) was added and the saturated sodium bicarbonate water after 3-minute churning was added. The methylene chloride washed the organic layer with saturated potassium bisulfate after extraction, and it dried with anhydrous sodium sulfate. Flash column chromatography refined the residue obtained by distilling off under a reduced pressure of a solvent, and the mark compound (77 mg) was obtained as a mixture of alpha and beta arrangement.

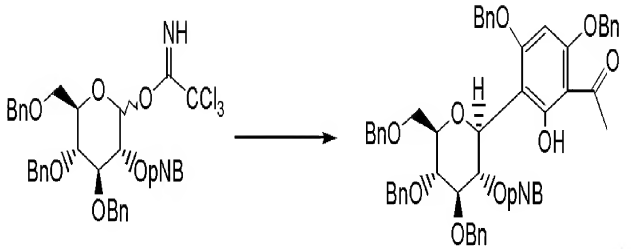
[0079]

NMR. ($CDCl_3$) :. 3.5-4.0(m,6H), 4.5-4.95(m,8H), 5.20(dd,0.75Hz,53Hz), 5.66(dd,0.25H,J=2.3Hz,54Hz), 7.1-7.2 (m,2H), 7.2-7.3(m,13H), 7.4-7.5(m, 2H, 8.1-8.2(m, 2H).

[0080]

Embodiment 6: Manufacture of 4,6-bis(benzyloxy)-2-hydroxy-3-(3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl beta-D-glucopyranosyl) acetophenone

[Chemical formula 49]



[0081]

3,4,5-tri-O-benzyl-1-O-. (2,2,2-trichloroethanimidoyl), [the methylene chloride (2 ml) solution of-2-O-p-nitrobenzyl D-glucopyranose (50 mg) and 4,6-bis(benzyloxy)-2-hydroxy acetophenone (40 mg)] -It is trimethylsilyl at 40 **. A trifluoromethanesulfonate (5microl) is added and it is ********** to a room temperature gradually. Ethyl acetate extracted, after adding saturated sodium bicarbonate water after churning at a room temperature for 1 hour. Flash column chromatography refined the residue obtained by distilling off a solvent under a reduced pressure after desiccation with anhydrous sodium sulfate, and 10 mg of mark compounds were obtained.

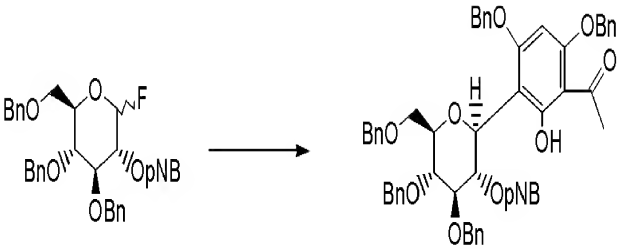
[0082]

NMR. ($CDCl_3$) :. 2.47(s,1.5H), 2.55(s,1.5H), 3.5-3.8(m,6H), 4.4-5.1(m,13H), 5.85(s,0.5H), 5.95(s,0.5H), 7.04 (d,2H,J=8.5Hz), 7.1-7.4(m,25H), 14.2 (s, 0.5H), 14.4(s, 0.5H).

[0083]

Embodiment 7: Manufacture of 4,6-bis(benzyloxy)-2-hydroxy-3-(3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl beta-D-glucopyranosyl) acetophenone

[Chemical formula 50]



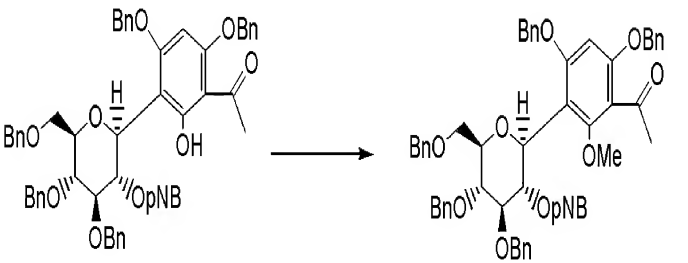
[0084]

3,4,5-tri-O-benzyl-1-O-. (2,2,2-trichloroethanimidoyl)-2-O-p-nitrobenzyl D-glucopyranosyl [the methylene chloride (1 ml) solution of a fluoride (56 mg) and 4,6-bis(benzyloxy)-2-hydroxy acetophenone (98 mg)] -Add BF_3 and OEt_2 (25microl) at 78 **, and it is ********** to a room temperature gradually. The methylene chloride extracted, after adding saturated sodium bicarbonate water after churning at a room temperature for 20 minutes. Flash column chromatography refined the residue obtained by distilling off a solvent under a reduced pressure after desiccation with anhydrous sodium sulfate, and 46 mg of the same mark compounds as Embodiment 6 were obtained.

[0085]

Embodiment 8: Manufacture of 4,6-bis(benzyloxy)-2-methoxy-3-(3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl beta-D-glucopyranosyl) acetophenone

[Chemical formula 51]



[0086]

In the solution of acetone (1.5 ml) of 4,6-bis(benzyloxy)-2-hydroxy-3-(3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl beta-D-glucopyranosyl) acetophenone (57 mg), K_2CO_3 (15 mg), Methyl iodide (214microl) was added and heating churning was carried out at 60 ** for 28 hours. The insoluble matter was filtered, flash column chromatography refined the residue produced by distilling off a solvent, and 27 mg of mark compounds were obtained.

[0087]

NMR. ($CDCl_3$) :. 2.37(s,1.5H), 2.47(s,1.5H), 3.5-3.8(m,9H), 4.2-5.1(m,13H), 6.23(s,0.5H), 6.24(s,0.5H), 6.95-7.05(m,2H), 7.15-7.45(m,25H), 7 . 85-7.95(m, 2H).

[0088]

Embodiment 9: Manufacture of 4,6-bis(benzyloxy)-2-methoxy-3-(3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl beta-D-glucopyranosyl) acetophenone

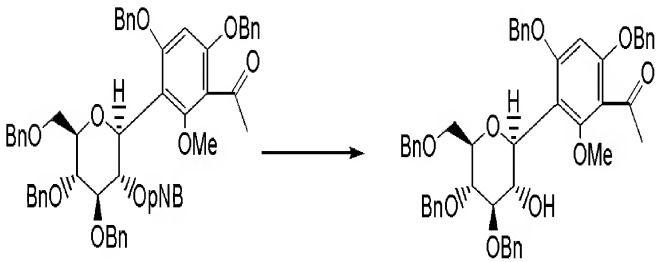
[0089]

It is NaH (22 mg) to the solution of the dimethylformamide (7 ml) of 4,6-bis(benzyloxy)-2-hydroxy-3-(3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl beta-D-glucopyranosyl) acetophenone (505 mg). Nujol and methyl iodide (1 ml) were added 60%, and heat churning was carried out at the room temperature for 40 minutes. It dried with the anhydrous sodium sulfate which washed the after-dilution organic layer with ethyl acetate. Flash column chromatography refined the residue produced by distilling off a solvent under a reduced pressure, and 256 mg of mark compounds which are the same compound as Embodiment 8 were obtained.

[0090]

Embodiment 10: Manufacture of 4,6-bis(benzyloxy)-2-methoxy-3-(3,4,5-tri-O-benzyl-beta-D-glucopyranosyl) acetophenone

[Chemical formula 52]



[0091]

A 4,6-screw. (Benzyloxy)-2-methoxy-3-. (3,4,5-tri-O-benzyl-2-O-p-nitrobenzyl beta-D-glucopyranosyl) To the isopropanol (7 ml) and the methanol (7 ml) mixed solvent of acetophenone (256 mg), a saturated ammonium chloride solution (1.9 ml), The end (640 mg) of indium was added and heating churning was carried out at 75 ** for 32 hours. After filtering an insoluble matter, it diluted with ethyl acetate, and 1N hydrochloric acid aqueous solution washed the organic layer, and it dried with anhydrous sodium sulfate. 174 mg of mark compounds were obtained by refining the obtained residue with flash column chromatography after solvent distilling off.

[0092]

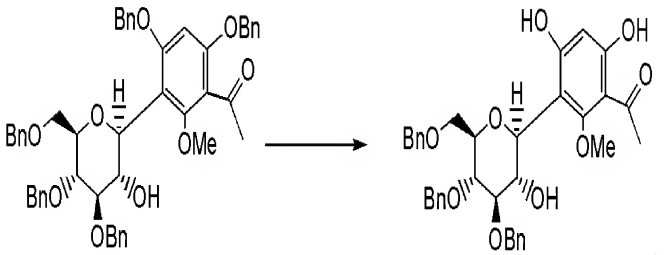
NMR($CDCl_3$): 2.46 (s, 3H), 3.5-3.8 (m, 9H), 4.4-5.1 (m, 11H), 6.35 (s, 1H), 7.2-7.5 (m, 25H).

IR(cm^{-1}): 3459, 2867, 1699, 1596, 1098.

[0093]

Embodiment 11: Manufacture of 4,6-dihydroxy-2-methoxy-3-(3,4,5-tri-O-benzyl-beta-D-glucopyranosyl) acetophenone

[Chemical formula 53]



[0094]

Add 10%Pd-carbon (22 mg) to the tetrahydrofuran (8 ml) solution of 4,6-bis(benzyloxy)-2-methoxy-3-(3,4,5-tri-O-benzyl-beta-D-glucopyranosyl) acetophenone (174 mg), and Under hydrogen gas atmosphere, The catalyst was filtered after agitating in ordinary pressure for 10 hours. 140 mg of mark compounds were obtained by distilling off under a reduced pressure of a solvent.

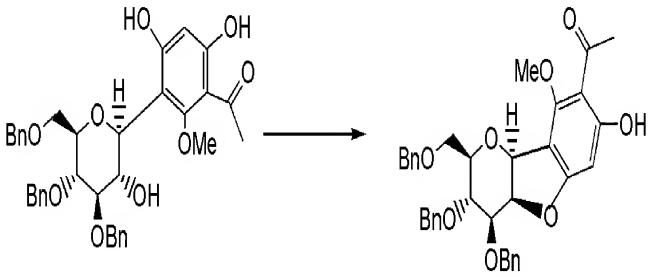
[0095]

NMR. ($CDCl_3$) :. 2.66(s,3H), 3.6-4.0(m,6H), 3.77(s,3H), 4.4-4.6(m,3H), 4.75-4.95(m,4H), 6.30(s,1H), 7.15-7.35 (m,15H), 8.55(br,s,1H), 12.99(s 1H.

[0096]

embodiment 12:1- {. (2 R,3 R,4 S,4aR, 9bS) Manufacture of-3,4-bis(benzyloxy)-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}ethanone

[Chemical formula 54]



[0097]

[the benzene solution (3 ml) of 4,6-dihydroxy-2-methoxy-3-(3,4,5-tri-O-benzyl-beta-D-glucopyranosyl) acetophenone (140 mg)] Tributyl phosphine (82microl) and 1,1'-azobis (N, N dimethylformamide) (57 mg) were added one by one under the room temperature, and were agitated for 5 hours. Flash column

chromatography refined reaction mixture as it was, and 101 mg of mark compounds were obtained as a colorless crystal.

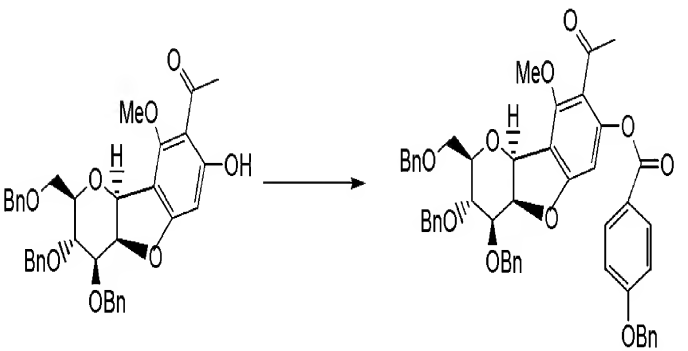
[0098]

NMR($CDCl_3$): 2.59(s,3H), 3.45-3.55(m,2H), 3.65-3.80(m,2H), 3.96(dd,1H,J=8.6Hz,4.7Hz), 4.14(s,3H), 4.47 (dd,2H,J=14Hz, 12Hz), 4.57(d,1H,J=13Hz), 4.61(t,1H,J=4Hz), 4.77(d,1H,J=12Hz), 4.85-4.90(m,2H), 5.12 (d,1H,J=4Hz), 6.24(s,1H), 7.2-7.4(m,6H) 14.07(s, 1H).

[0099]

embodiment 13:1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-7-(p-benzyloxy benzoyloxy)-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl} ethanone

[Chemical formula 55]



[0100]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) In the methylene chloride (1 ml) solution of methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl} ethanone (38 mg), p-benzyloxy benzoyl . Chloride (16 mg) and 4-(N,N-dimethyl) aminopyridine (10 mg) were added at the room temperature, and were agitated for 1 hour. Flash column chromatography refined then and 45 mg of mark compounds were obtained.

[0101]

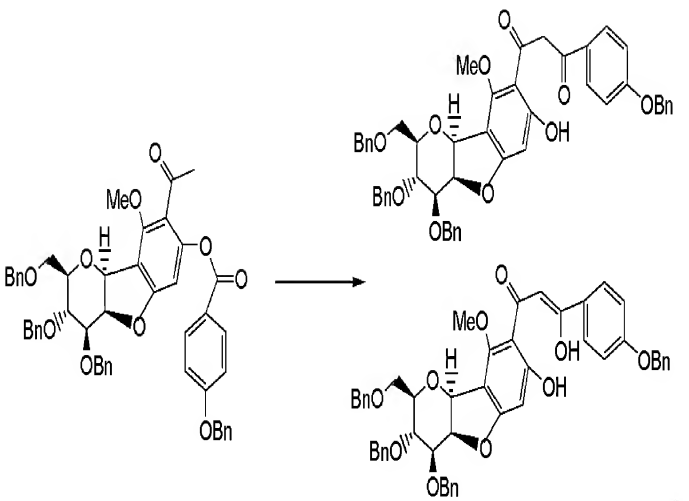
NMR. ($CDCl_3$) :. 2.44(s,3H), 3.5-3.6(m,2H), 3.7-3.8(m,2H), 3.97(dd,1H,J=9Hz,5Hz), 4.06(s,3H), 4.49(s,2H), 4.59(d,1H,J=11Hz), 4.64(t,1H,J=4 Hz), 4.77 (d, 1H, J= 12 Hz), 4.85-4.95 (m, 2H), 5.1-5.15 (m, 3H), 6.56 (s, 1H), 7.02 (d, 2H, J= 9 Hz), 7.2-7.5 (m, 20H), 8.06(d, 2HJ = 9 Hz).

[0102]

embodiment 14:1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-(4-benzyloxyphenyl)-1,3-propanedione

(However, a mark compound is obtained as a mixture of the tautomer)

[Chemical formula 56]



[0103]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy), [the tetrahydrofuran solution (1 ml) of methyl]-7-(p-benzyloxy benzoyloxy)-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO / 3,2-/ [b] [1] benzofuran-8-yl}ethanone (45 mg)] It added to the tetrahydrofuran solution (0.5 ml) of lithium diisopropylamide beforehand prepared from diisopropylamine (78microl) and n-butyl lithium (0.56mmol) at -30 **, and it agitated for 1 hour, keeping temperature at -30 ** from -20 **. The saturated ammonium chloride solution was added and ethyl acetate extracted. It dried with anhydrous sodium sulfate after washing with the saturation sodium chloride aqueous solution, and the organic layer distilled off the bottom solvent of a reduced pressure. Flash column chromatography refined the obtained residue and 32 mg of mark compounds were obtained.

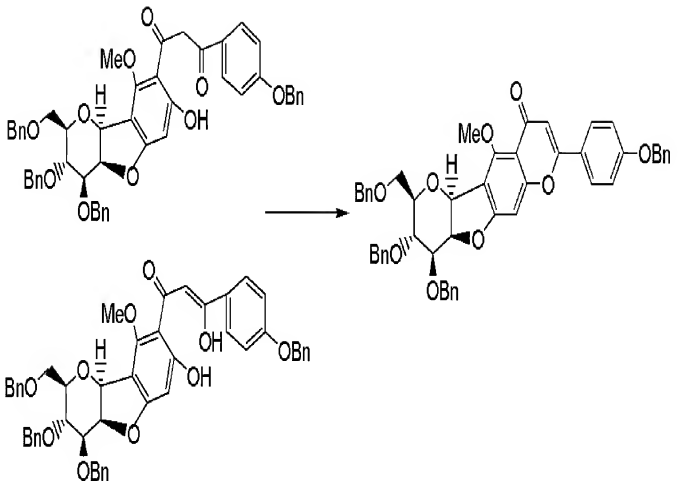
[0104]

NMR($CDCl_3$): 3.4-3.8(m,4H), 3.81(s,1H), 3.85-4.0(m,1H), 4.05(s,2H), 4.3-4.9(m,7H), 5.0-5.1(m,1H), 5.13 (s,2H), 6.24(s, 0.34H), 6.32(s,0.66H), 7.02(d,2H,J=9Hz), 7.2-7.5(m,20H), 7.85(d,1.32H,J=9Hz), 7.92(d,0.66H, J=9Hz), 13.16(s,0.66H), 13.89(s, 0.34H, 15.62(s-0.66H).

[0105]

Embodiment 15:. (2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy)-2-[(benzyloxy) methyl]-8-[4-(benzyloxy) phenyl]-11-methoxy-3,4,4a,11 -- manufacture of b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 57]



[0106]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) The mixture of methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-(4-benzyloxyphenyl)-1,3-propanedione and its tautomer. To the methylene chloride solution (0.8 ml) of (23 mg), it is trimethylsilyl at a room temperature. Tori Flatow (7microl) was added and it agitated for 10 minutes. After adding saturated sodium bicarbonate water, the organic layer obtained by a methylene chloride extracting was dried with anhydrous sodium sulfate. After distilling off a solvent, 14 mg of mark compounds were obtained by refining with flash column chromatography.

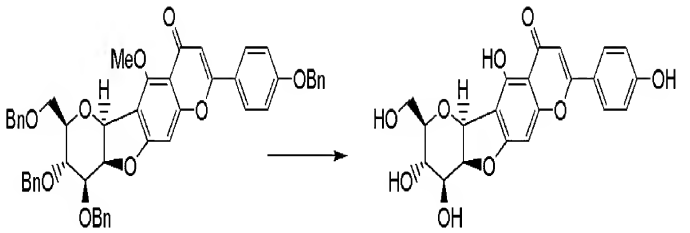
[0107]

NMR($CDCl_3$): 3.5-3.85(m,4H), 4.00(dd,1H,J=9Hz,5Hz), 4.12(s,3H), 4.47(s,2H), 4.63(d,1H,J=11Hz), 4.68(t,1H, J=4Hz), 4. 8-4.95(m,3H), 5.14(s,2H), 5.18(d,1H,J=3Hz), 6.55(s,1H), 6.78(s,1H), 7.07(d,2H,J=9Hz), 7.2-7.45 (m,20H), 7.80(d.2H,J=9Hz).

[0108]

Embodiment 16:. (2 R,3 S,4 S,4aS, 11bS)-3,4,11-trihydroxy 2-hydroxymethyl-8-[4-hydroxyphenyl]-3,4,4 a,11 -- manufacture of b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 58]



[0109]

(2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) Methyl]-8-[4-. (Benzyloxy) phenyl]-11-methoxy-3,4,4a,11 -- b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON (14 mg) -- a room temperature -- the methylene chloride solution (1M.) of $BCl_3$0.5 ml was added and the saturated sodium bicarbonate water after 10 minutes was added. The depositing solid matter was dissolved in methanol (2 ml), the methylene chloride solution (1M, 0.5 ml) of BCl_3 was added to this under ice-cooling, and it agitated at the room temperature for 20 minutes. After dissolving the residue obtained by distilling off the bottom solvent of a reduced pressure in O= 0.5 ml of MeOH/AcOH/H_2/1 ml/one ml, It refined in HPLC (ODS negative-phase column: gradient elution from CH_3CN/H_2O=20/80 to CH_3CN/H_2O=84/16), and 0.7 mg of mark compounds were obtained.

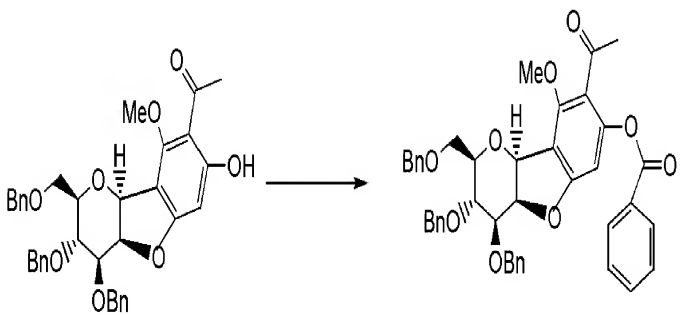
[0110]

NMR (CD_3) OD):3.3-3.4(m,1H), 3.55-3.65(m,2H), 3.82(dd,1H,J=2Hz,12Hz), 3.99(dd,1H,J=5Hz,10Hz), 4.68 (t,1H,J=4Hz), 5.20 (d, 1H, J= 3 Hz), 6.64(s,1H), 6.65(s1H), 6.89(d,2H,J=9Hz), 7.85(d,2H,J=9Hz).

[0111]

embodiment 17:1- {. (2 R,3 R,4 S,4aR, 9bS) Manufacture of-7-benzoyloxy 3,4-bis(benzyloxy)-2-[(benzyloxy) methyl]-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}ethanone

[Chemical formula 59]



[0112]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}ethanone (46 mg) and benzoyl Chloride (11microl) is used, It was operated like Embodiment 13 and 50 mg of mark compounds were obtained.

[0113]

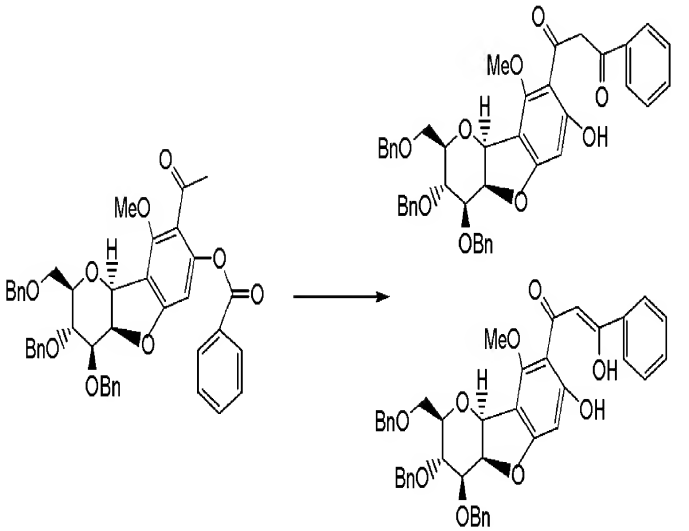
NMR. ($CDCl_3$) :. 2.45(s,3H), 3.5-3.6(m,2H), 3.7-3.8(m,2H), 3.98(dd,1H,J=5Hz,9Hz), 4.07(s,3H), 4.50(s,2H), 4.59(d,1H,J=11Hz), 4.65(t,1H,J=4 Hz), 4.78 (d, 1H, J= 12 Hz), 4.85-4.95 (m, 2H), 5.14 (d, 1H, J= 4 Hz), 6, 56 (s, 1H), 7.2-7.55 (m, 17H), 7.61 (t, 1H, J= 7 Hz), 8.11(d, 2H, J= 7 Hz).

[0114]

embodiment 18:1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-phenyl-1,3-propanedione

(However, a mark compound is obtained as a mixture with the tautomer)

[Chemical formula 60]



[0115]

1- {. 2R, 3R, and 4S -- 4 aR, A 9bS-7-benzoyloxy 3,4-screw. (Benzyloxy) Using the mixture (50 mg) of-2-[(benzyloxy) methyl]-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}ethanone and its tautomer, with the same operation as Embodiment 14. 35 mg of mark compounds were obtained.

[0116]

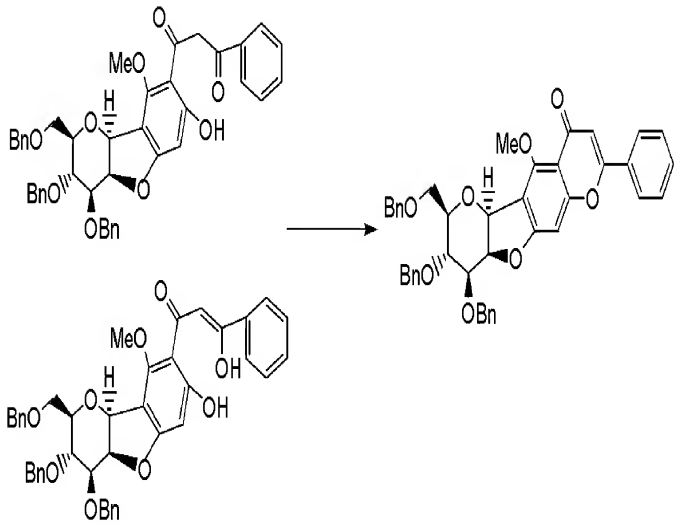
NMR. ($CDCl_3$) :. 3.4-3.8(m,4H), 3.78(s,1.5H), 3.9-4.0(m,1H), 4.07(s,1.5H), 4.3-4.9(m,7H), 5.03(d,0.5H, J=4Hz), 5.10(d, 0.5H, J= 4 Hz, 7.2-7.6(m,18H), 7.85-8.0(m,2H), 13.14(s,0.5H), 13.87(s,0.5H), 15.41(s,0.5H).

[0117]

Embodiment 19 :

(2R, 3S, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-11-methoxy-8-phenyl-3,4,4 a,11b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 61]



[0118]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) The mixture (35 mg) of methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-phenyl-1,3-propanedione and its tautomer is used, The same operation as Embodiment 15 was performed, and 8 mg of mark compounds were obtained.

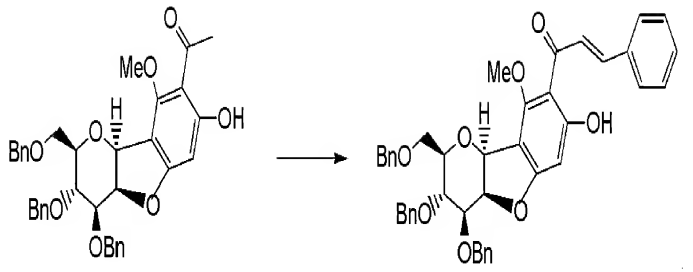
[0119]

NMR($CDCl_3$): 3.5-3.75(m,3H), 3.83(t,1H,J=9Hz), 3.95-4.05(m,1H), 4.13(s,3H), 4.47(s,2H), 4.63(d,1H, J=11Hz), 4.68(t, 1H,J=4Hz), 4.82(d,1H,J=12Hz), 4.85-4.95(m,2H), 5.20(d,1H,J=3Hz), 6.65(s,1H), 7.2-7.6 (m,18H), 7.85-7.9(m,20H).

[0120]

embodiment 20:1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-phenyl-2-propene-1-ON

[Chemical formula 62]



[0121]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) To the dioxan solution (0.8 ml) of methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}ethanone (20 mg), benzaldehyde (3.8microl). And the NaOH aqueous solution (0.8 ml) was added at the room temperature 50%, and it agitated for 4 hours. After it added 15 ml of 1N hydrochloric acid aqueous solutions and ethyl acetate extracted, the solvent was distilled off after desiccation with anhydrous sodium sulfate. Flash column chromatography refined the obtained residue and 18 mg of mark compounds were obtained.

[0122]

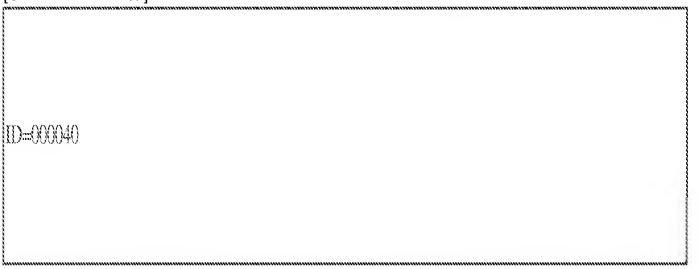
NMR. ($CDCl_3$) :. 3.5-3.8(m,4H), 3.97(dd,1H,J=5Hz,9Hz), 4.07(s,3H), 4.4-4.6(m,3H), 4.64(t,1H,J=4Hz), 4.7-4.9 (m,3H),5.11 (d, 1H, J= 4 Hz), 6.32(s,1H), 7.2-7.5(m,18H), 7.6-7.7(m,2H), 7.79(s,2H), 13.95(s,1H).

IR(NaCl, film, cm^{-1}): 2861, 1628, 1558, 1454.

[0123]

embodiment 21:1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-(4-methylphenyl)-2-propene-1-ON

[Chemical formula 63]



[0124]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy), [the dioxan solution (1.6 ml) of-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO / 3,2-/ [b] [1] benzofuran-8-yl}ethanone (42 mg)] The same reaction as Embodiment 20 was performed using 4-methylbenzaldehyde (8.2microl), and 30

mg of mark compounds were obtained.

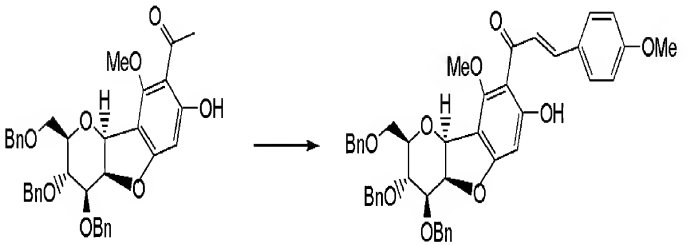
[0125]

NMR($CDCl_3$): 2.38(s,3H), 3.5-3.8(m,4H), 3.97(dd,1H,J=5Hz,9Hz), 4.06(s,3H), 4.45-4.50(m,2H), 4.58(d,1H, J=11Hz),4. 64(t,1H,J=4Hz), 4.75-4.9(m,3H), 5.11(d,1H,J=4Hz), 6.32(s,1H), 7.2-7.45(m,17H), 7.50(d,2H, J=8Hz), 7.76(d,2H,J=2Hz), 13.99(s, 1H.

[0126]

embodiment 22:1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-(4-methoxypheny)-2-propene-1-ON

[Chemical formula 64]



[0127]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy), [the dioxan solution (1.6 ml) of-2-[(benzyloxy) methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO / 3,2-/ [b] [1] benzofuran-8-yl}ethanone (42 mg)] The same reaction as Embodiment 20 was performed using 4-methoxy benzaldehyde (9.4microl), and 37 mg of mark compounds were obtained.

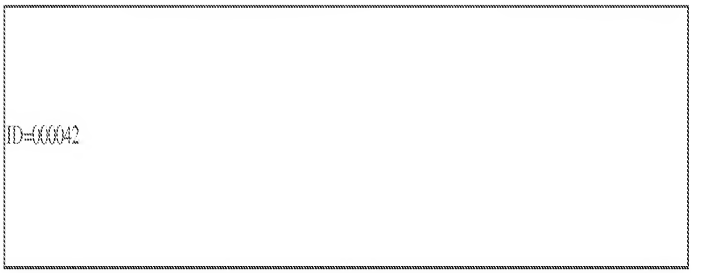
[0128]

NMR($CDCl_3$): 3.5-3.8(m,4H), 3.87(s,3H), 3.97(dd,1H,J=5Hz,9Hz), 4.06(s,3H), 4.45-4.50(m,2H), 4.58(d,1H, J=11Hz),4. 63(t,1H,J=4Hz), 4.75-4.9(m,3H), 5.11(d,1H,J=4Hz), 6.32(s,1H), 6.92(d,2H,J=9Hz), 7.2-7.4 (m,15H), 7.55(d, 2H, J= 9 Hz, 7.68(d,1H,J=15Hz), 7.78(d,1H,J=15Hz), 14.06(s,1H).

[0129]

Embodiment 23:. (2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-11-methoxy-8-phenyl-3,4,4 a,11b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 65]



[0130]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) The DMSO solution of methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-phenyl-2-propene-1-ON (18 mg). The DMSO (100microl) solution of iodine (0.30 mg) was added to (0.4 ml), and it heated at 150 ** for 1 hour. The hypo aqueous solution washed the organic layer after dilution with ethyl acetate, and the solvent was distilled off under the reduced pressure after desiccation with anhydrous sodium sulfate. Flash column chromatography refined the obtained residue and 5 mg of mark compounds were obtained. The instrumental-analysis data of this compound was completely in agreement with the compound obtained in Embodiment 19.

[0131]

Embodiment 24:. (2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-11-methoxy-8-phenyl-3,4,4 a,11b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

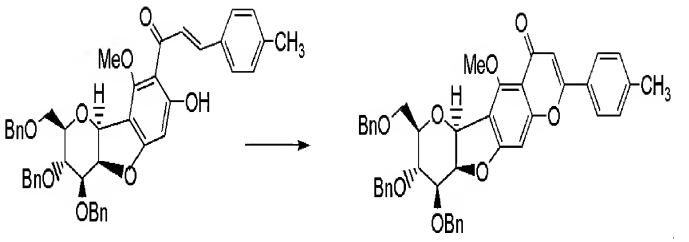
[0132]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) Methanol of methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-phenyl-2-propene-1-ON (17 mg). (1 ml) After adding iodobenzene diacetate (17 mg) to a solution further in addition to the bottom of ice-cooling of the methanol (180microl) solution of KOH (16 mg), it heated at the room temperature for 2 hours. The hypo aqueous solution washed the organic layer after dilution with the methylene chloride, and the solvent was distilled off under the reduced pressure after desiccation with anhydrous sodium sulfate. Flash column chromatography refined the obtained residue and 5 mg of mark compounds were obtained. The instrumental-analysis data of this compound was completely in agreement with the compound obtained in Embodiment 19.

[0133]

Embodiment 25:. (2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-8-(4-methylphenyl)-11-methoxy-3,4,4 a,11b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 66]



[0134]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) Methanol of methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-(4-methylphenyl)-2-propene-1-ON (30 mg). (2.1 ml) Using the solution, the same reaction as Embodiment 24 was performed, and 14 mg of mark compounds were obtained.

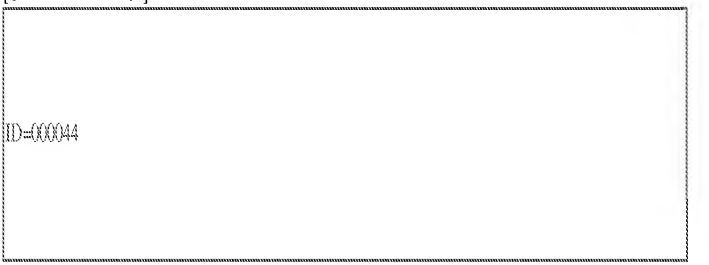
[0135]

NMR($CDCl_3$): 2.42(s,3H), 3.5-3.75(m,3H), 3.82(t,1H,J=9Hz), 4.00(dd,1H,J=5Hz,9Hz), 4.12(s,3H), 4.47(s,2H), 4.63(d, 1H,J=11Hz), 4.68(t,1H,J=4Hz), 4.82(d,1H,J=12Hz), 4.85-4.95(m,2H), 5.19(d,1H,J=3Hz), 6.61(s,1H), 6.79(s, 1H, 7.2-7.4(m,15H), 7.42(d,2H,J=7Hz), 7.75(d,2H,J=8Hz).

[0136]

Embodiment 26:. (2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy) Manufacture of-2-[(benzyloxy) methyl]-11-methoxy-8-(4-methoxypheny)-3,4,4 a,11b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 67]



[0137]

1- {. (2R, 3R, 4S, 4aR, 9bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) Methyl]-7-hydroxy-9-methoxy-3,4,4 a,9b-tetrahydro 2H-PIRANO [3,2-] [b] [1] benzofuran-8-yl}-3-(4-methoxypheny)-2-propene-1-ON. Using the methanol (2.5 ml) solution of (37 mg), the same reaction as Embodiment 24 was performed, and 9 mg of mark compounds were obtained.

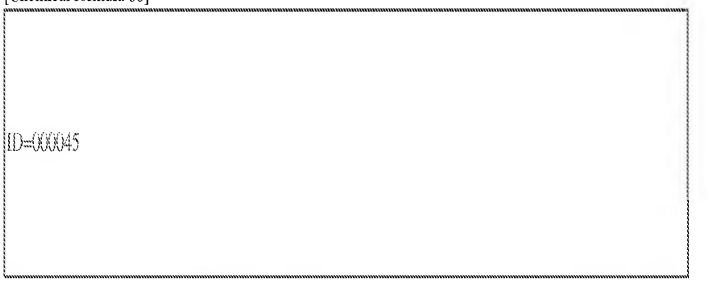
[0138]

NMR($CDCl_3$): 3.5-3.75(m,3H), 3.82(t,1H,J=9Hz), 3.88(s,3H), 4.00(dd,1H,J=5Hz,9Hz), 4.12(s,3H), 4.47(s,2H), 4.63(d, 1H,J=11Hz), 4.68(t,1H,J=4Hz), 4.83(d,1H,J=12Hz), 4.85-4.95(m,2H), 5.19(d,1HmJ=3Hz), 6.56(s,1H), 6.78(s, 1H, 7.00(d,2H,J=9Hz), 7.2-7.45(m,15H), 7.81(d,2H,J=9Hz).

[0139]

Embodiment 27: (2 R,3 R,4 S,4aR, 11bS) Manufacture of -3,4,11-trihydroxy 2-hydroxymethyl-8-phenyl-3,4,4 a,11b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 68]



[0140]

(2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy)-2-[(benzyloxy) methyl]-11-methoxy-8-phenyl-3,4,4 a,11b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON (8 mg) is used, The same operation as Embodiment 16 was performed, and 0.7 mg of mark compounds were obtained.

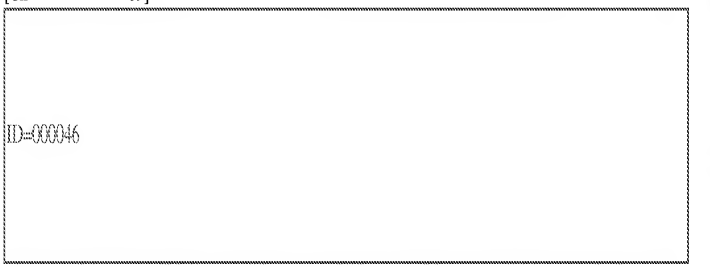
[0141]

NMR (CD_3) OD):3.3-3.4(m,1H), 3.55-3.65(m,2H), 3.82(dd,1H,J=3Hz,12Hz), 3.99(dd,1H,J=5Hz,9Hz), 4.7-4.75 (m,1H), 5.22 (d, 1H, J= 3 Hz), 6.70(s,1H), 6.81(s,1H), 7.5-7.6(m,3H), 7.95-8.05(m,2H).

[0142]

Embodiment 28:. (2 R,3 R,4 S,4aR, 11bS)-3,4,11-trihydroxy 2-hydroxymethyl-8-(4-methylphenyl)-3,4,4 a,11 -- manufacture of b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 69]



[0143]

(2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy)-2-[. (Benzyloxy) Methyl]-11-methoxy-8-. (4-methylphenyl)-

3,4,4 a,11 -- the methylene chloride solution (0.5 ml) of b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON (14 mg) -- the methylene chloride solution (1 -- M solutions) of bottom BCl_3 of ice-cooling 1

ml was added and methanol (4 ml) was added after churning for 10 minutes. The bottom solvent of a reduced pressure was distilled off, methanol (10 ml) and 1N hydrochloric acid aqueous solution (10 ml) were added to residue at the room temperature, and it agitated for 45 hours. After distilling off under a reduced pressure of methanol, 5.1 mg of mark compounds were obtained by reversed phase chromatography's refining the solution obtained by adding acetic acid (7 ml), and freeze-drying the fraction containing an object.

[0144]

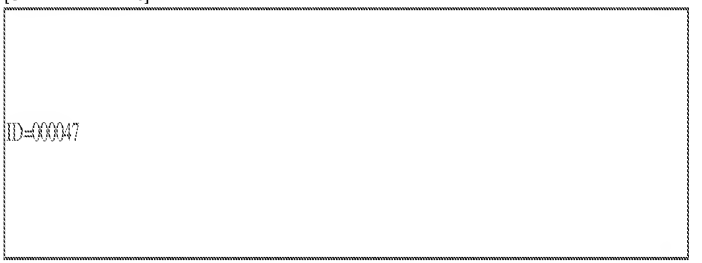
NMR (CD_3) OD):2.42(s,3H), 3.3-3.4(m,1H), 3.55-3.65(m,2H), 3.82(dd,1H,J=2Hz,12Hz), 3.99(dd,1H,

J=5Hz,9Hz), 4.65-4.7 (m, 1H), 5.22(d,1H,J=3Hz), 6.67(s,1H), 6.75(s,1H), 7.34(d,2H,J=8Hz), 7.88(d,2H, J=8Hz).

[0145]

Embodiment 29:. (2 R,3 R,4 S,4aR, 11bS)-3,4,11-trihydroxy 2-hydroxymethyl-8-(4-methoxypheny)-3,4,4 a,11 -- manufacture of b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 70]



[0146]

(2R, 3R, 4S, 4aR, 11bS) A-3,4-screw. (Benzyloxy)-2-[(benzyloxy) methyl]-11-methoxy-8-(4-methoxypheny)-3,4,4 a,11b-tetrahydro 2H,10H-PIRANO [2',3':4,5] Flo [3,2-] [g] chromene 10-ON (9 mg) is used, 4.3 mg of mark compounds were obtained by performing the same operation as Embodiment 28.

[0147]

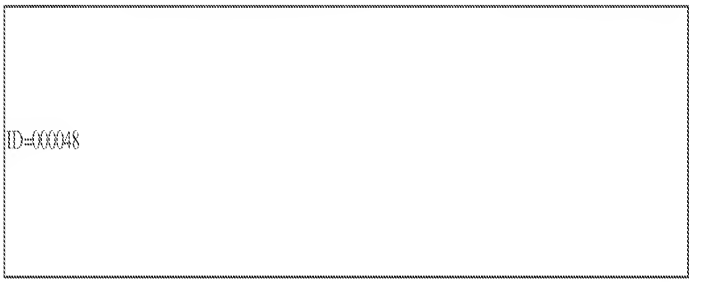
NMR(DMSO-d_6): 3.2-3.25(m,1H),3.3-3.45(m,2H), 3.6-3.7(m,1H), 3.8-3.9(m,4H), 4.44(t,1H,J=6Hz), 4.6-4.65

(m,1H),5.01(d, 1H,J=5Hz), 5.09(d,1H,J=3Hz), 5.39(d,1H,J=6Hz), 6.80(s,1H), 6.96(s,1H), 7.13(d,2H,J=9Hz), 8.07(d,2H,J=9Hz), 13.5(s,1H).

[0148]

Embodiment 30:. The (2 R,3 R,4 S,4aR, 11bS)-3,4,11-tris (acetyloxy)-2-[(acetyl OKISHISHI) methyl]-10-oxo 8-phenyl- 3,4,4a, 11b-tetrahydro 2H and 10H - PIRANO[2', 3':. Manufacture of 4,5] Flo [3,2-] [g] chromene 10-ON

[Chemical formula 71]



[0149]

. [(2 R,3 R,4 S,4aR, 11bS)-3,4,11-trihydroxy 2 PIRANO / - hydroxymethyl-8-phenyl-3,4,4 a,11b-tetrahydro 2H,10H-/ [2',3':4,5] Flo / 3,2-/ [g] chromene 10-ON] To the pyridine (100microl) solution of (1 mg), dimethylamino pyridine (2 mg) and acetic anhydride (5microl) were added at the room temperature, and were agitated for 20 minutes in it. It distilled off under the reduced pressure of a solvent and the mark compound was obtained by refining residue with silica gel column chromatography.

[0150]

NMR. ($CDCl_3$) :. 2.01(s,3H), 2.07(s,3H), 2.17(s,3H), 2.48(s,3H), 3.75-3.85(m,1H), 4.0-4.1(m,1H), 4.26(dd,1H, J=5Hz,12Hz), 4.88(dd,1H,J=5Hz) 5.15 (d, 1H, J= 5 Hz), 5.28 (t, 1H, J= 9 Hz), 5.39 (dd, 1H, J= 5 Hz, 10 Hz), 6.59 (s, 1H), 7.45-7.55 (m, 3H), 7.8-7.9(m, 2H).

[0151]

Embodiment 31: Powder of the compound obtained in Embodiment 27

The compound 1g, the lactose 865g, and 100 g of corn starch which were obtained in Embodiment 27 were mixed with the blender, and powder was obtained.

[0152]

Embodiment 32: The cutaneous sensitization inhibition test of the mouse using the compound obtained in Embodiment 27

The abdominal part of a BALB/c mouse (7 - 9-week old, maleness; Charles River Japan) is shaved with mite electric clippers (made by the Daito electricity industrial company), Sensitization was carried out by doing 100microl spreading of 7%2,4,6-trinitro 1-chlorobenzene (7%TNCB-acetone: olive-oil =4:1). The right ear-pinna table bladder was made to cause cutaneous sensitization six days after sensitization by applying TNCB (1%TNCB-acetone: olive-oil =1:9) every [10micro / 1] (total 20mul) 1%. The specimen material was suspended and administered orally to the 0.5% hydroxypropylcellulose solution 30 minutes before inducement and 6 hours and 21 hours afterward (each seven groups). Evaluation measured auricular thickness with the DEJIMA tic indicator (product made from Mitsutoyo) 24 hours an inducement front and after after inducement, and made the difference the ear-pinna tylosis. Betamethasone valerate was used as a positive control medicine.

[0153]

The result was shown in drawing 1. As shown in the figure, remarkable ear-pinna hypertrophy was caused by applying TNCB to the ear pinna of the mouse which carried out sensitization by TNCB. As a result of

administering orally the compound obtained in Embodiment 27, the ear-pinna tylosis in a mouse cutaneous sensitization model was controlled by the dosage dependence target, and the statistical study significant difference ($p<0.05$;Dunnett'test) was accepted in the 2 microg [more than]/kg dosage.

[0154]

[Effect of the Invention]

As explained above, the new flavone derivative provided by this invention has anti-inflammatory activity and an antiallergic action handle, and has the inhibitory effect especially outstanding in mouse cutaneous sensitization.

It is useful as a treating agent of an inflammatory disease and an allergic disease.

Especially the antiallergic effect is excellent and useful as physic for prevention of atopic dermatitis, cutaneous sensitization, etc., or a therapy.

[Brief Description of the Drawings]

[Drawing 1]Drawing 1 is a figure showing the result of Embodiment 32.

[Translation done.]